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PHYSICIANS OF THE MACHINE AGE*

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HUMANITY has entered a new era. As we speak of the Bronze Age or the Iron Age, we must today speak of the Machine Age. André Siegfried, the distinguished French political philosopher, has recently reminded us that Europeans are disposed to call it also the American Age. For, if it was in Europe that the principles of modern large-scale production were conceived, it was in the United States that they were first put into practice completely and whole-heartedly. This places heavy requirements of leadership on the American people for shaping the human consequences of this new era; it makes unique demands upon the American physician.

The physical sciences and technology which have created this machine age have altered profoundly the task of the physician. They have faced him with new and challenging responsibilities. Fortunately, the achievements of the physical sciences have enabled modern medicine to meet this challenge more effectively. From chemistry and physics the medical scientist has gained knowledge and instruments for his own spectacular discoveries in the cause and cure of disease. Technology has made possible our organized efforts for the treatment of human ills.

Through organic evolution—slowly acting over countless centuries—man acquired his natural powers; he became adapted to a limited environment. Gradually he learned to supplement curiosity with the powers of observation and reason and association. Finally, with the advent of the Baconian era of experimental science he developed special technics for unravelling the causes of things, so that he might establish conclusions "useful for man's life and knowledge." Thus man has extended his natural powers.

Among the first fruits of that scientific era came clearer understanding of the nature of our bodies and of the relation of our life to our environment. The microscope revealed the structure of the living organism for the care of which the physician is responsible. Machines for the production of

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roentgen-rays disclosed the interior of the body and created a new epoch in diagnosis. Electronic amplifiers now make it possible to observe the subtle functions of the nervous system and to probe the mysterious workings of the brain. The electron microscope brings viruses within the range of human vision. The cyclotron and the atomic pile which gave us a new, dread agent of destruction also provide radio-active elements with which to trace the chemical processes of life.

These are but a few examples of how the machines of our scientific age extend the sensitivity and the range of human senses. By such devices we have established an entirely new sensory relationship to our environment. These instruments have broadened the intellectual horizons of man. They have enabled the physician to understand more fully the mechanisms of the body. Because of that he has been able to aid men to resist more effectively the invisible agents of disease—to aid men to meet more adequately the forces of their environment.

These forces are no longer merely natural in origin. Through instrument-aided senses the scientist has gained a clearer insight into nature. Thus he has been stimulated to the invention of new machines for human power. By these our voice is carried around the world. The power of a hundred thousand horses is held under the control of a finger—capable of releasing men from the bondage of labor. Machines carry us swiftly across the land, under the sea and through the air. By machines we have created our own environments, without regard for natural heat or cold, and light or darkness.

It is not my purpose to recount the brilliant, but familiar, achievements of modern science. It is my purpose to emphasize the biological usefulness of scientific effort. It is to remind you that the curiosity of scientists will continue to create new conditions, amidst which the lives of men must be lived. If physicians do not direct the course of our machine age, so that it satisfies more perfectly the biological needs of men, I must ask you: Who is there capable of doing so?

Machines should be created for the aid of men. If they have any useful function, it is to increase the natural powers of the human body. Unfortunately, engineers know little of how the body works and physicians are unable to design machines. Because of this dichotomy of social functions, the biological basis of machines has been generally ignored, and life has been less wholesome than it might have been.

These problems were brought into sharp focus by the needs of war. Out of our common peril there was reborn respect for men and their biological needs. Machines assumed their proper rôle as instruments for their users rather than as mere objectives of an industrial civilization. It was then quite obvious that gun-sights and bomb-sights are aids to vision; that submarines are devices for sustaining life below the seas; that aeroplanes were created to give men the power to travel swiftly in three dimensions. To achieve these purposes more effectively, physicians and engineers formed

a natural partnership. In the Armored Forces Medical Laboratory, in the Naval Medical Research Institute and in the Aeromedical Laboratory of the Army Air Forces Material Command physicians studied the biological suitability of instruments and machines. New designs were guided by the physicians' knowledge of the mechanisms and the requirements of the human body. Under their direction anthropologists adapted the dimensions of seats and turrets and controls to the structure of the body as well as to the convenience of the engineer. Physiologists and ophthalmologists designed lighting systems for boats and tanks and planes so as to protect night vision. Pathologists re-designed structures responsible for injuries in crashes.

Out of this close partnership also came a clearer realization that new powers provided by machines may place new stresses on the body. There are three clear instances of this in the spectacular advance of aviation.

The history of this advance is a long record of man's restless urge to overcome his physiological restrictions. It first appears in mythology and ancient literature as a desire for the birds' freedom from the gravitational tie to earth. But when in 1783 man was at last freed from his earth-bound life he was only started on the conquest of his aerial limitations.

Driven by the urge for greater range of action, man's mechanical ingenuity devised means for ascent to ever higher altitudes—to which he had not been adapted by the slow process of evolution. Finally in 1862, Glaisher, an English meteorologist, and Coxwell, his balloon engineer, reached the limits of human survival. They went to a reported altitude of over five miles. There Glaisher became unconscious and both would have perished, had not Coxwell, paralyzed though he was, seized the valve cord in his teeth and released the gas by vigorously nodding his head. On recovering consciousness, Glaisher voiced man's faith in the power of science to break the bounds of human limitations: "I certainly shall not take it upon myself," said he, "to set the limits of human activity and indicate the point, if it exists, where nature tells the aeronaut: 'You shall go no further'."

I have retold this classic account of a physiological limitation on the use of aerial machines because it was overcome by a medical scientist. By studying the reactions of the human body to high altitudes Paul Bert found that unconsciousness and death are there due to a lack of oxygen. From then until now, physicians have been partners in the development of high altitude flight by following in the footsteps of Paul Bert and prescribing the oxygen necessary for life.

This was one of the major functions of the medical services of the air forces during this war. Each airman was carefully instructed in the physiology of high altitudes. The medical services designed modern equipment that would deliver enough oxygen to meet the fliers' needs at any height. Physicians carefully watched the aerial operations for signs of harmful effects on the personnel. Engineers and physicians together made it possible for our airmen to fly their great bombing missions over the Nazi's European fortress.

Ultimately the skill of engineers threatened new hazards to the body. Anti-aircraft fire reached higher; but engine superchargers met the challenge, and carried our planes still higher. Finally, at 38,000 feet the pressure of the atmosphere becomes so low that even pure oxygen delivered to the lungs was not sufficient adequately to load the blood. There life became impossible. Machines had once again exceeded the physiological powers of those for whom they had been constructed. Once more physicians and engineers pooled their knowledge, and the pressurized cabin was created. In those sealed enclosures, air compressed to give the airmen adequate oxygen and warmth. In those machines a natural environment has been restored to fliers, at altitudes unsuitable for life.

Two of the primary requirements for good fighter-craft are high speed and great maneuverability. These are the characteristics which enable them to excel in plane-to-plane combat, to evade the heavier fire-power of larger craft, and to give effective protection to bomber missions. Engineers and metallurgists worked for years to develop such planes that can withstand the centrifugal forces of high-speed turns and the pull-out from a power dive.

The engineers succeeded, but the machines they created could not be flown by men. For our cardiovascular system was not evolved to pump blood made five to ten times as heavy by a suddenly applied centrifugal force. Under these conditions, blood accumulates in the lower extremities and in the viscera. The result is an inadequate supply of oxygen to the brain. Gray-out, then black-out of vision are the first effects, and loss of consciousness follows. To help the human body meet these stresses imposed by swift combat planes, physicians designed anti-acceleration suits which aid the heart, by preventing the pooling of blood in the lower parts of the body. Without such a device the engineers' creation is but a futile object, unsuitable for use in the hands of a blind or unconscious pilot.

Artificial wings and powerful motors have freed men from the age-old restriction of gravitational forces. But the new machine forces act upon the body of the pilot as well as upon the artificial wings. The force which holds the plane in a banked turn, or in a loop, excites the gravity receptors, the tension receptors in the muscles and the tendons, and the nervous endings in the semicircular canals which detect rotation. These sensory pathways are then stimulated by the resultant of this machine-exerted force and that of the earth's gravitational field. Because the sensory mechanism is unable to resolve these two components of the stimulating force, a true sense of orientation in space is lost. The false sense of position must then be corrected by visual reference to the earth. And so, when clouds or darkness interfere, the pilot becomes incapable of maintaining a desired course relative to the surface of the earth. That was all that could be said about the matter in the first World War.

Finally, however, physicians determined the causes of man's inaptitude for directed flight without visual contact with the earth. It was then possible to devise instrumental aids and flight through clouds and darkness

became safe and commonplace. Once again the physiological characteristics of the flier had limited his full utilization of his aircraft; once again physicians defined the need and physicists provided instruments to supplement the senses. By the artificial horizon and the bank-and-turn indicator and by radar the machine was adapted to man and the scope of human flight was once again increased.

What we have done to adapt the machines of war to the needs of those who fought in our defense can be done for the machines of peace. We are probably at the beginning of an era of great scientific and industrial development. It will be a human tragedy if physicians and biologists do not sit in the councils of those who shape the instruments and the environments of man. All about us we can see the unhappy consequences of a great industrial civilization, created without adequate regard for the biological requirements of physical and mental health. Millions who come together in cities to use the machines of industry live under the pall of an unnatural atmosphere polluted by the products of the machine. Death stalks the highways at night in high-powered vehicles illuminated with disregard of the facts of vision. Machine-made noise is the constant lot of those who cannot escape to a more natural environment. But these are not necessary faults of the machines—for machines are as we make them. We can build them for our use or for our harm.

Physicians, who understand the variability of individuals, realize that it is impossible to design machines which satisfy equally well the needs of all men. This is especially true of the complicated tools of modern industry. The use of specialized machines requires special qualities of body and mind. It thus becomes necessary to fit men to machines as well as machines to men.

After physicians and engineers had done the best they could to design the machines of war for the men who must use them, physicians selected the men who were best suited to the machines. By visual tests, night fighter pilots were separated from day fighters; on the basis of their physical characteristics, submarine crews were differentiated from the crews of surface craft; a low tolerance of anoxia disqualified a man from high altitude flying; and poor physical fitness removed a soldier from an armored tank to non-combatant service.

The machines of industry are likewise suited to various types of human organisms. The rolling mill in a steel plant and the typewriter in an office are both useful tools. But a man who can manipulate the typewriter may be quite unable to operate the rolling mill. Or the manual dexterity required to drive a truck is inadequate for a tool-maker. The ingenuity of the engineer will surely increase the number and variety of machines. They will frustrate men or they will increase his powers for useful achievement, depending upon how effectively the physician selects those who are physically qualified for their operation.

The diversity of machines also provides a remarkable opportunity to the physician who is concerned with the physical and mental rehabilitation of

those who have lost some of their normal physiological powers. If machines can be designed to give the average man undreamed of ability to travel with the speed of sound, or see across the oceans and blast apart the mountains, surely it is not too much to hope that the maimed and weak can be equipped to play a useful rôle in modern industry. Among the diversified machine operations of the future there can be some machine suited to the physical ability of each worker. Instruments and machines can overcome the broken body's limitations and restore the patient's usefulness and self-respect. This should be a powerful aid to the physician in the care of the sick and wounded. To achieve this objective, we must have the understanding coöperation of engineers and industrialists—and the directing wisdom of the physician.

Gloomy prophets of the machine age have long predicted that work would become a mechanical round of monotonous boredom. We must admit that some of the joy of craftsmanship has been lost, but we cannot deny that many are being freed from dull, debasing labor. Galley-slaves and those who toiled from dawn to dusk to build the pyramids have been replaced by skilled operators of machines. But the machines are useful only to those who have the necessary skills and mental fitness. With increasing specialization in modern industry, there is, accordingly, a growing need for the selection of those who are psychologically suited to each special task.

Some industries have proved the profit of this practice. But it was under the compelling stimulus of a machine war that the medical service of the Army Air Forces gave the clearest demonstration of its value. Physicians combined physical and psychological examinations in an over-all assessment of the fitness of an individual. Selection was first made of those best suited for duties on the ground or in the air. From among the latter, men were then chosen for the several special tasks of pilot, bombardier, navigator, gunner. The results were remarkable. In the case of one large control group their assessed fitness was disregarded and they were assigned to a duty by chance or preference. At the end of their training it was found that those who would have been excluded from duty as a pilot had three times as many accidents as those who would have been assigned. Furthermore, of those who had been judged to be best qualified for their duties only 4 per cent were disqualified for poor performance in their work. On the other hand, 80 per cent of those who would have been barred from training were ultimately "washed-out" on the basis of poor achievement. Such was the proof that it is possible to avert the prevalent human wastage of square men in round machines.

Democracy demands freedom in choice of occupation. But the success of an industrial democracy requires also that the worker shall have expert guidance in his choice of that occupation for which he is mentally and temperamentally fitted. A misplaced worker cannot use his machine to good advantage, and society is the loser.

The direct impact of machines on men in war and industry is but one aspect of a changing pattern of life in the machine age.

Science frees men from the hazards of ignorance and the uncontrolled domination of natural forces, but science and technology also create a complex civilization that severely taxes the biological capacities of the individual citizen. Each new scientific discovery that provides men with new powers creates new human problems and new dangers. We cannot, and we would not, retreat out of the scientific civilization we have created, and we cannot stand still. Either we will increase our understanding of the forces which shape our lives, and use them to our advantage or we shall fall victims to uncontrolled powers.

Scientific discovery is the exploration of the unknown, and I, for one, do not see how it is possible to direct an explorer through unknown territory. Because of this no man can plan or predict the future of civilization. But it is possible to modify its course and shape new developments to the benefit of men. The internal combustion engine that carries bombers on their missions of destruction is the same engine that cultivates the fields for starving millions. The slums of modern cities blight the lives and dwarf the spirits of men. But the same machines that build the slums can recreate the cities for human welfare. The aerial transportation that makes more difficult the control of epidemic diseases is also available for the swift transportation of sick and wounded.

The machine age will be as we make it. Science gives us the building stones of a better world. If our primary concern is for the machine and the power of machines, it will be a world in which flesh and blood are less real than paper and ink and celluloid and steel.

The blast of the atomic bomb awakened men to an awareness of the human implications of the forces controlled through science. The time is ripe to supplement the generous instinct for human welfare with aggressive action by those who are familiar with the biological needs of men. Only thus will it be possible to give men a life of usefulness and purpose— with machines as their tools for biologically and spiritually significant accomplishments.

For this great humanitarian task of fitting the Machine Age to the biological needs of men there is no one better fitted than the physician.

RHEUMATIC PNEUMONIA *

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Introduction

The interpretation of pulmonary lesions in rheumatic fever has had a complex history. Originally the lung had been considered, on clinical grounds, to be one of the major foci of rheumatic activity; the discovery of a primary lesion in the heart, together with more careful pathological study of the lungs, has led to the realization that in many cases the lesions previously diagnosed as rheumatic pneumonia were actually due to cardiac failure or to such complications as infarction, atelectasis or intercurrent infection. In some quarters the pendulum has swung completely in the other direction and the existence of a pulmonary component of the rheumatic process has been categorically denied.[7] Nevertheless, careful investigations by a number of different observers [29, 19, 21, 9, 13, 18] have led to the recognition of a characteristic pathological picture which is not attributable to any of the above-mentioned complications and occurs only in the presence of rheumatic activity. Although the term "rheumatic pneumonia" has been assigned to this pathological condition, its precise relationship to rheumatic fever is still obscure.

At least four hypotheses may be advanced to explain the etiology of this process. Some workers [8, 9] feel that the lesions observed are specific manifestations of rheumatic activity in the lungs, just as Aschoff bodies represent rheumatic activity in the heart. Indeed, Gouley and Fraser have reported the presence of Aschoff bodies in these pulmonary lesions—an observation not confirmed by a number of other investigators. Furthermore, the individual lesions regarded as specific (alveolitis, mononuclear infiltration, hyaline pseudomembrane, etc.) have since been recognized as the common expressions of a variety of distinct pathological conditions. In the light of this work, the thesis that rheumatic pneumonia is a specific manifestation of active rheumatic fever remains unproved on the basis of available pathological data.

The possibility that the pulmonary changes are purely secondary to congestive heart failure constitutes a second hypothesis. Epstein and Greenspan [4] have carefully investigated this possibility and found, in 23 cases of acute and chronic coronary arterial disease in which death was due to cardiac failure and in 16 cases of hypertensive heart disease with failure, that "the only changes in the lungs were chronic ones characteristic of long-

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standing pulmonary congestion." That the presence of mitral stenosis does not confer this characteristic picture upon the pulmonary manifestations of congestive heart failure is indicated by the fact that these investigators found no hyaline membranes in the lungs of 20 cases of mitral stenosis in which death was due to unrelated causes or to chronic heart failure. It seems, therefore, that cardiac failure per se, even when associated with chronic valvular lesions, cannot account for the anatomical features which have been labeled rheumatic pneumonia.

It is highly unlikely that intercurrent infection during the course of rheumatic fever is responsible for these pulmonary changes: pathogenic organisms cannot be isolated from the sputum; the roentgen-ray appearance is diffuse rather than segmental; and the clinical picture is not typical of bacterial pneumonia.

Finally, it has been suggested that a *combination* of rheumatic activity and cardiac failure might be responsible for the pathogenesis of the lesions. Hadfield [13] concluded that the primary lesion of the rheumatic lung is a "widespread fibrinous alveolitis," which may be *converted* in the presence of dyspnea, probably of cardiac origin, into the characteristic pattern of rheumatic pneumonia. Epstein and Greenspan ascribe this pattern to a combination of diffuse rheumatic vasculitis and dyspnea, most likely due to heart failure.

There is good general agreement concerning the pathological features of rheumatic pneumonia, even though the etiology of these lesions is undetermined, but the clinical manifestations of this condition are still the subject of controversy. The object of the present study is to establish criteria by means of which a clinical and roentgen-ray diagnosis of rheumatic pneumonia might be ventured.

Review of the Literature

I. *Pathological*

The older literature on rheumatic pneumonia has been reviewed by Paul,[23] Howard [14] and Epstein and Greenspan.[4] Most of the reports prior to 1920 were not accompanied by autopsy verification and therefore cannot be evaluated. Within the last two decades, a more precise investigation of the pathology has resulted in a fairly well-established anatomical description of the disease. Only the major contributions to this description will be noted here, as exhaustive reviews of the pathological literature have been made by Epstein and Greenspan [4] and Neubuerger, Geever, and Rutledge.[22]

The gross picture has been stated by many observers [20, 12, 18, 11, 19] to be characteristic. The lung has an "india rubber-like," resistant consistency and its surface is mottled with focal hemorrhages. More reliable criteria for diagnosis, however, are the microscopic features, which may be considered under five main categories:

(1) *Alveolar walls and interstitial tissues.* Naish [21] described thickening of the alveolar walls by the proliferation of endothelial cells, some fibroblasts, and occasional polymorphonuclear leukocytes. This is a constant feature of the disease which has been observed by all investigators. Engorgement of the capillaries has also been repeatedly noted. Gouley [11] stressed the edema of the interstitial tissues in the early phases. In studying the evolution of the lesion he noted [12] that in the chronic stages the alveolar walls and septal interstitial tissues were thickened by a proliferation of fibrous and elastic tissue which was at times extensive enough to restrict the vascular bed and which, in association with arteriosclerosis of the smaller vessels, gave rise to right-sided heart failure in the absence of mitral disease.

(2) *Intraluminal exudate.* Naish first described the hemorrhagic nature of the alveolar exudate. In the early stages of the disease, Paul [23] noted a hemorrhagic and fibrinous exudate which later underwent organization with the formation of casts of loose fibrous tissue within the bronchioles. Edema was often a constituent of the exudate. The presence in the exudate of polymorphonuclear leukocytes in small numbers has been described by many observers.[21, 11, 18] The mononuclear, occasionally multinuclear cells which are most characteristic of the alveolar exudate have been considered phagocytic cells of the reticulo-endothelial system. Gouley [11] described two types of such cells appearing in succession: the foamy endothelial cell present initially was followed by a larger basophilic cell of the "Aschoff" type. The cells which covered the organized exudate within the respiratory bronchioles and alveolar ducts have been designated as alveolar epithelium [18] or as alveolar septal cells.[22] In the "chronic" stages the thickened alveolar walls are lined by cuboidal cells which Gouley [11] considered to be epithelial.

(3) *Hyaline pseudomembrane.* Masson, Riopelle, and Martin [18] described a pseudomembrane which covered the walls of the respiratory bronchioles, obstructing the mouths of, but not actually filling, the alveolar structures. This membrane was thought to be the result of a transformation of fibrinous exudate occurring at the periphery of the lung, where mobility is great, while deeper in the lung, where mobility is less, it became organized by connective tissue, as Paul had described earlier. Hadfield observed that the hyaline fibrinous membrane was similar to that found in many infectious processes (influenza, streptococcal pneumonia, pneumonic plague, etc.) and also in newborn infants whose lungs contained aspirated amniotic fluid. Farber and Wilson [6] demonstrated experimentally that forceful inspiratory effect could produce membranes of similar distribution when there was fluid within the respiratory tree. Hadfield felt that the rheumatic process affected primarily the alveoli and alveolar ducts, resulting in a fibrinous exudate, which was then transformed into a hyaline membrane as a result of dyspnea, probably of cardiac origin.

(4) *Vascular lesions.* In cases of rheumatic carditis, von Glahn and Pappenheimer [29] described changes in the systemic and pulmonary arterioles consisting of fibrin deposition within and about each involved vessel, de-

structive changes and cellular reaction in the vessel wall, and perivascular infiltration by inflammatory cells; these changes later undergo organization. Paul [23] described lesions involving all coats of the arterioles: there were swollen, foamy cells in the intima, pyknotic nuclei in the media, and round cell accumulations in the perivascular zones with thrombi often present in the lumen. In the later stages, there was hyalinization of the intima, scarring of the media, and perivascular fibrosis. Gouley has emphasized the presence of hyaline thrombi in the capillaries of the alveolar walls in the acute stages.

(5) *Aschoff bodies.* Investigators have long searched for Aschoff bodies in the lung. Fraser [8] and Gouley and Eiman [9] reported finding them while others found none.[15, 4, 19, 18, 20, 12, 17, 21]

II. *Clinical*

These pathological findings have served as a basis upon which two fairly distinct clinical syndromes have evolved. The first type was described by Rabinowitz [25] in 1926, and, with but minor variations, has been reiterated by many subsequent observers (Howard,[14] Naish,[21] Gouley,[10] and others). In general, the pulmonary symptoms were said to develop insidiously, without upper respiratory infection or chill. Toxicity was not marked and the temperature was reported variously as only slightly elevated,[21, 25] or moderate to high.[10] Gouley felt that the height of the temperature was more a reflection of the severity of the general rheumatic infection than of the pulmonary involvement. The respiratory symptoms were usually slight, consisting of a hacking cough productive of small amounts of sputum which was usually blood-streaked and never purulent.* Concomitant pleurisy was inconstantly observed. There was no respiratory distress. In contrast to the paucity of pulmonary symptoms, the physical signs were striking and almost diagnostic. Throughout the literature there is a recurring emphasis on the presence of signs of a fleeting pneumonitis: areas of slight dullness, fine râles, and tubular breathing, which tended to be evanescent, reappearing in the same area or in other parts of the lung.[25, 1, 27] The prognosis was apparently unaffected by the pulmonary complication.

Both Hadfield and Gouley separated from the above group a second clinical category—"a small group of patients in whom the pulmonary invasion is extremely rapid and widespread, accompanied by quickly developing dyspnea and cyanosis" [10]—which may terminate fatally. Coburn,[1] Tragerman,[28] Ravenna,[26] and Debré and his co-workers [3] have presented detailed reports on autopsied cases which were characterized clinically by an abrupt onset of profound respiratory distress out of all proportion to the physical findings. In contrast to the severe dyspnea and cyanosis present, physical signs in the chest were completely absent except terminally in many of the reported cases. Pyrexia was moderate to marked, cough was usually

* Rabinowitz is the only observer who has mentioned the rare occurrence of purulent sputum, but none of his cases was autopsied.

associated with the production of scanty blood-streaked sputum, and heart failure was a variable accompaniment. The outcome was usually fatal in days to weeks. The great similarity between acute pulmonary edema and this form of the disease has led Debré et al. to refer to it as an "acute inflammatory edema of rheumatic origin."

III. *Roentgenological*

Search of the literature reveals a dearth of descriptions and reproductions of roentgenograms of rheumatic pneumonia. With but one exception, the only illustrations are those of Coburn.[1, 2] Only one of these was from a pathologically proved case; it exhibited a diffuse haze throughout both lungs which seems indistinguishable from the roentgen appearance of pulmonary edema. Poynton and Schlesinger's [24] reproduction, which Gouley considered illustrative of the rapid regression of rheumatic pneumonia, was more likely an instance of massive pericardial effusion with secondary compression atelectasis.

Brief descriptions of the roentgenographic features are furnished by Rabinowitz, Gouley, and Neubuerger, Geever and Rutledge. Rabinowitz found that chest roentgenograms were of value only in ruling out bronchopneumonia. Gouley [10] describes roentgen changes consistent with cardiac failure, but ascribes these to rheumatic pneumonia in view of their rapid spread or regression on serial roentgenograms. Corresponding to the migratory nature of the physical signs, Neubuerger et al. have also encountered changes resembling "pulmonary congestion" with some frequency, but in one case noted "widely disseminated fine stippling and mottling," which in association with a suitable clinical picture was considered suggestive of rheumatic pneumonia.

In general, despite the non-specific terminology and inadequacy of detail in the descriptions, and the lack of photographic reproductions, these reports suggest that the roentgen features more closely resemble the changes of cardiac failure than those of pneumonia.

Materials and Criteria

The pathological criteria enumerated above for the diagnosis of rheumatic pneumonia have been employed (figures 1 to 5). A clinical and roentgenological analysis has been made of six cases which at autopsy manifested the characteristic anatomical features of rheumatic pneumonia. In an attempt to evaluate the incidence of rheumatic pneumonia as well as other pleuro-pulmonary complications in chest roentgenograms, a series of 100 episodes of acute rheumatic fever in 91 patients admitted to the New Haven Hospital from 1937 through 1945 has been studied. Three of the six cases verified at autopsy are included in this group; the other three occurred after the close of the period studied. Despite the fact that all of these patients had at least one chest roentgenogram, there was no element of

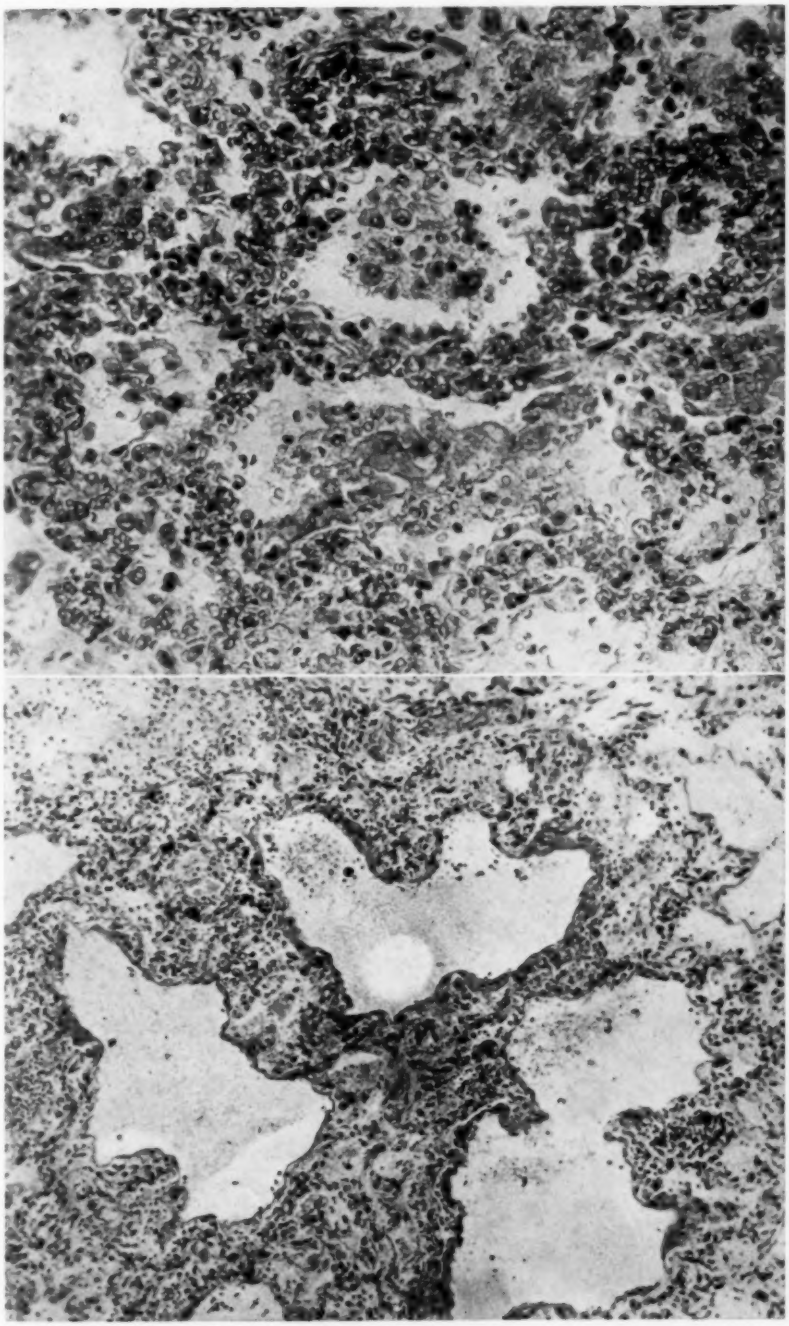


FIG. 1 (*above*). *Case 2.* J. P. Alveolar walls thickened by mononuclear cells; capillary congestion; exudate of mononuclear cells and a few red blood cells. Hematoxylin-eosin. × 250.

FIG. 2 (*below*). *Case 3.* R. M. Respiratory bronchioles and alveolar ducts lined by eosinophilic pseudomembrane that obstructs the mouths of adjacent alveoli; protein precipitate present. Hematoxylin-eosin. × 93.

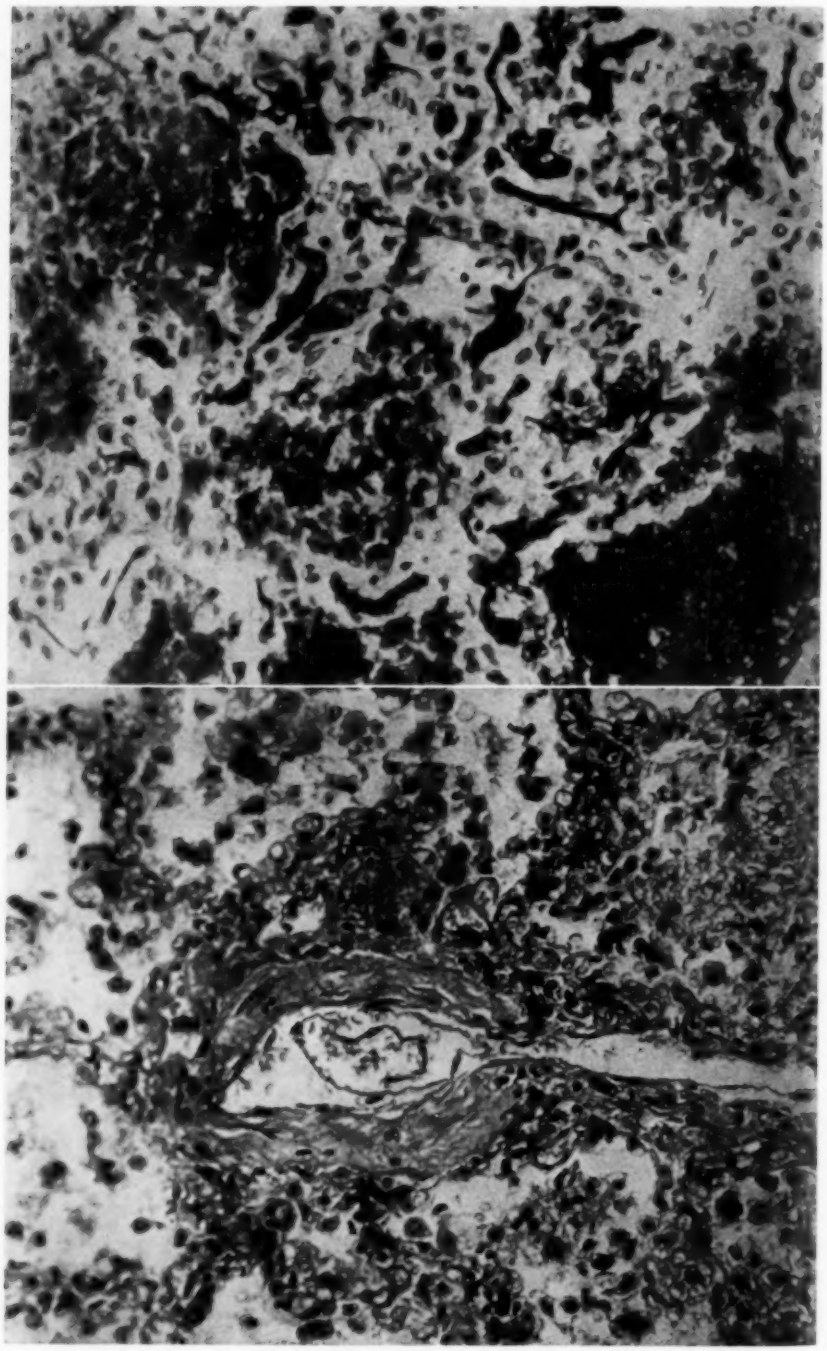


FIG. 3 (*above*). *Case 3.* R. M. Hyaline thrombi, appearing black in photograph, in alveolar capillaries; lumen of alveoli filled with red blood cells. Phosphotungstic acid-hematoxylin. × 420.

FIG. 4 (*below*). *Case 1.* A. G. Small branch of pulmonary artery: hyaline thickening of wall with loss of smooth muscle cells; scattered leukocytic nuclear fragments present. Hematoxylin-eosin. × 300.

selection inasmuch as roentgenographic examination is part of the routine investigation of cases of acute rheumatic fever. Throughout this study, the clinical criteria which have been used to establish the diagnosis of acute rheumatic fever were those enumerated by Jones.[15]

Case Reports

Case 1. A. G., a white female, 23 years of age, was first admitted to the New Haven Hospital on July 16, 1938, with a past history of acute rheumatic fever in 1933, followed by an interval of good health until eight months before admission, when an attack of the "grippe" left in its wake a dry cough. A month before admission the cough became productive of small amounts of blood-streaked white sputum, and the patient was troubled with intermittent left chest pain, probably pleuritic. The sudden onset of severe breathlessness the day before admission led to her hospitalization.

Physical Examination: On admission, the temperature was 101°, pulse 132 and respirations 28. The significant findings included the classical signs of mitral stenosis and insufficiency. Some dullness, but very few râles were elicited. The liver was not felt; there was no peripheral edema.

Course: Chest films on admission revealed widespread pulmonary infiltration (figure 6), which resolved completely within 10 days (figure 7). Save for the temperature elevation on admission, the patient's three week hospital course was afebrile. The white blood count remained at about 20,000 throughout and repeated throat and blood cultures were negative. Shortly after admission, respiratory symptoms and signs disappeared, and except for the appearance of a migratory arthralgia on July 19, her hospital stay was uneventful, and she was discharged with a diagnosis

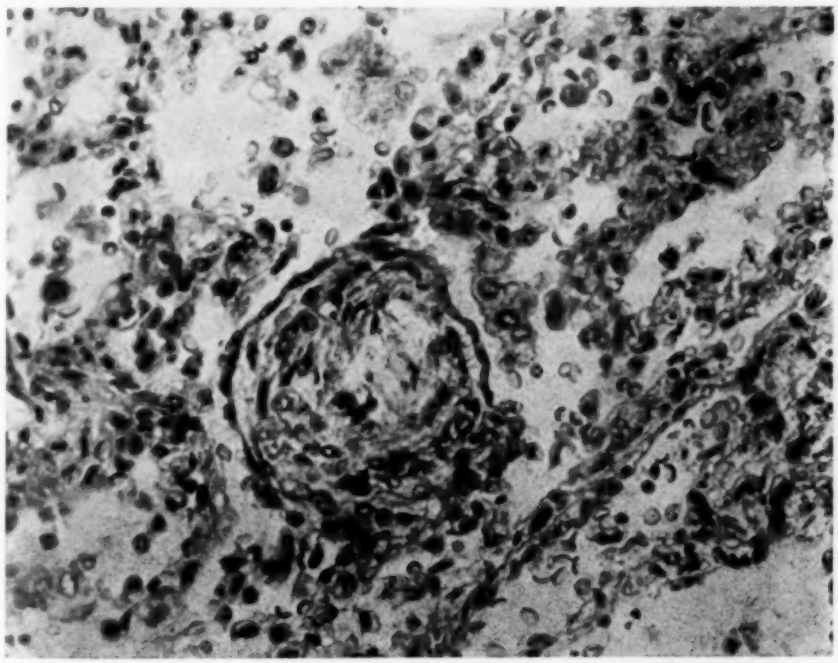
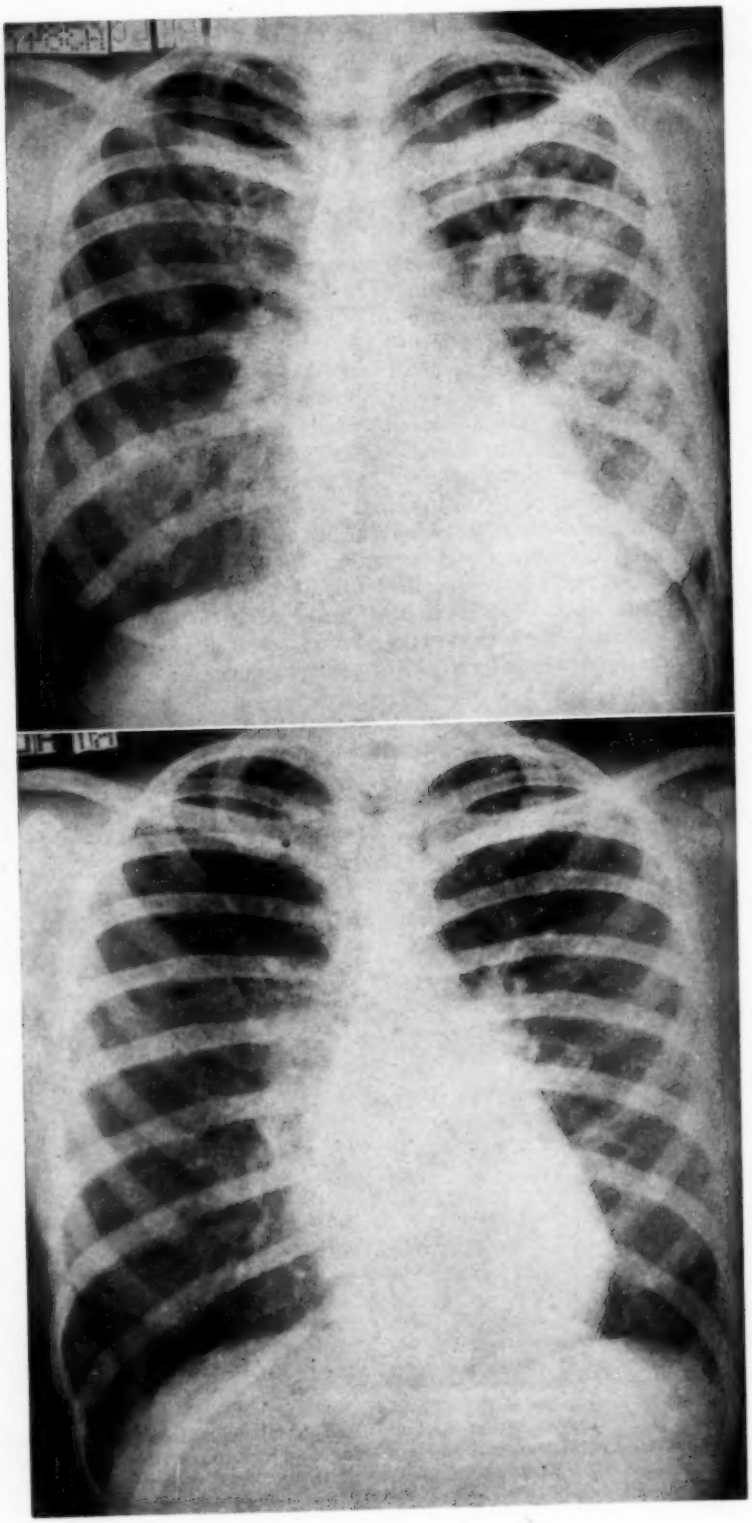


Fig. 5. *Case 2.* J. P. Organization within lumen of alveolus forming connective tissue mass covered by cells resembling epithelium. Hematoxylin-eosin. × 390.



of chronic and active rheumatic heart disease, with mitral stenosis and insufficiency, and ? rheumatic pleurisy and pneumonia.

Interval Note: Following discharge from the hospital on August 4, 1938, the patient was troubled by intermittent left pleurisy with fever, cough occasionally productive of blood-streaked sputum, fleeting joint pain, and dyspnea on exertion unrelieved by digitalization.

On Nov. 22, 1939, cough, chest pain, shortness of breath, and orthopnea starting abruptly 20 hours before admission and progressing rapidly to profound dyspnea, led to hospitalization.

Physical Examination: On admission, the temperature was 103°, pulse 104, and respirations 44. Patient was dyspneic, orthopneic, and cyanotic. Dullness and many fine and medium moist râles were present at the right base and over the right midchest anteriorly. The liver was not felt. There was no peripheral edema.

Course: Chest films on admission revealed a multilobar infiltration, more severe on the right (figure 8); repeat films in 10 days again showed complete clearing. On November 23, the day after admission, circulation time was 16 sec. (arm to tongue using 5 c.c. of decholin) and venous pressure was 10.5 cm. (needle 5 cm. below angle of scapula)—findings which were not in keeping with a diagnosis of severe heart failure. The leukocytosis (32,000 on admission) gradually subsided. Within four days the temperature returned toward normal, but a low grade fever and tachycardia persisted throughout. Sulfapyridine was given from November 24 to 28 without apparently influencing the course. Sputum on admission yielded B-hemolytic streptococci on mouse inoculation. Subsequent cultures of the sputum were negative.

The clinical course was attributed to a combination of acute heart failure, active rheumatic fever, and pneumonia.

Interval Note: Patient was followed in the Cardiac Clinic. Her course was characterized by periods of dyspnea and tachycardia, interspersed with asymptomatic intervals. On May 23, 1945, the abrupt onset of profound dyspnea, orthopnea, and cough with blood-streaked sputum 48 hours before admission led to her third and last hospitalization. The presence of persistent tachycardia, elevated sedimentation rate, weakness and debility over the preceding winter had led to a diagnosis of subacute rheumatic fever, and one month before admission intermittent right pleural pain appeared.

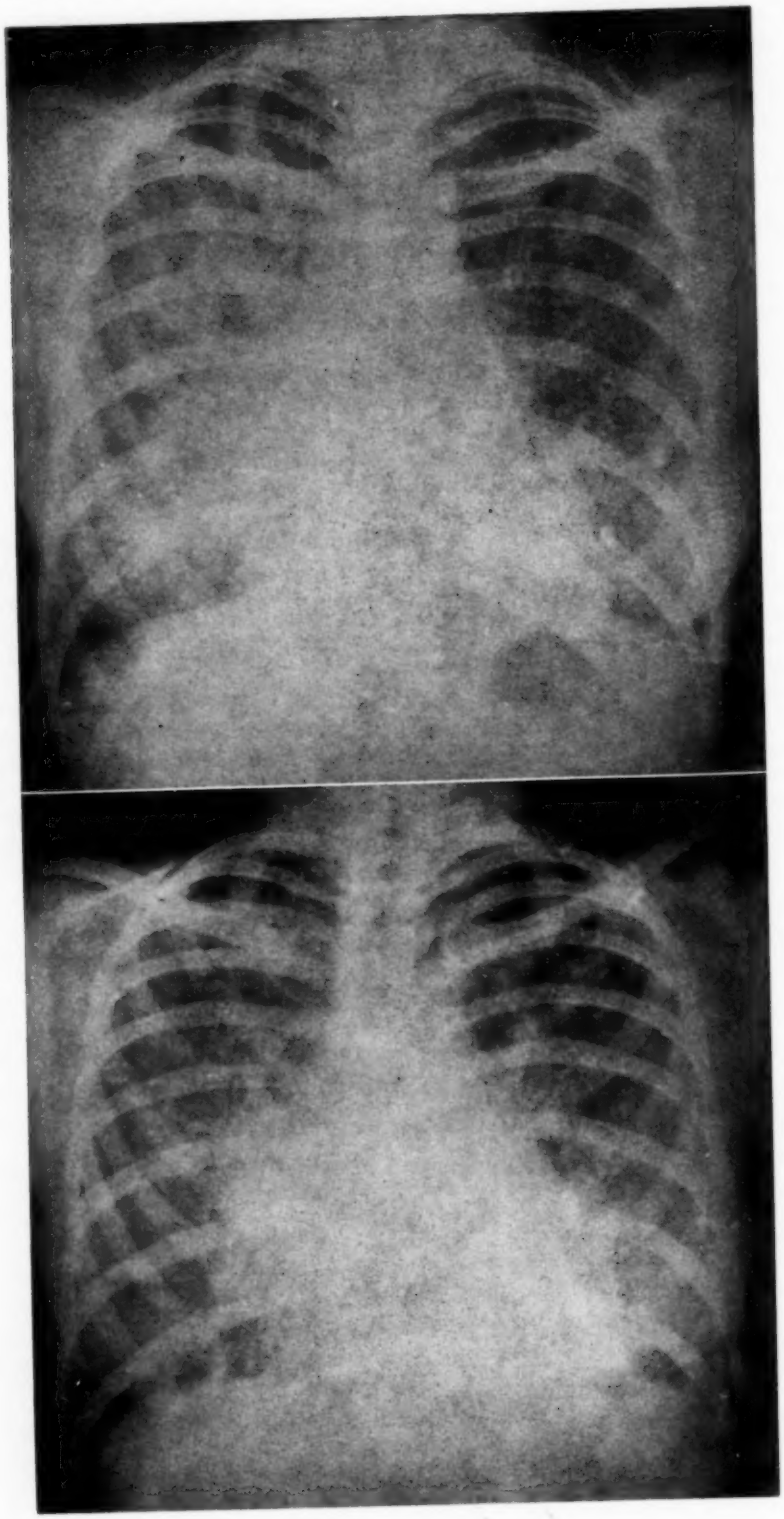
Physical Examination: Patient was desperately dyspneic, orthopneic and cyanotic. Temperature 104.8°, pulse 106, respirations 44. Save for a few rhonchi the chest was clear. The liver was not felt. No peripheral edema.

Course: On admission, roentgen-ray examination revealed an extensive pulmonary infiltration throughout both lung fields (figure 9), which remained essentially unchanged on serial reëxaminations. Leukocytosis and fever persisted throughout. Throat and sputum cultures were negative. Despite the persistence of marked respiratory distress (necessitating oxygen), no pulmonary physical signs ever developed. The patient died two weeks after admission.

Necropsy: There was a hydrothorax of 100 and 150 c.c. on the left and right sides respectively. Dense fibrous adhesions were present at the left base. The heart weighed 320 grams, with hypertrophy of the right ventricle and left auricle, and mitral and aortic stenosis. A few Aschoff bodies were present in the myocardium. The liver weighed 1610 grams and was the seat of marked passive congestion.

FIG. 6 (*above*). *Case 1.* A. G., age 23, female. Patchy areas of finely granular, hazy infiltration, penetrated by coarse linear streaks, are irregularly dispersed throughout both lung fields. This appearance is indistinguishable from pulmonary edema. The heart exhibits a mitral configuration.

FIG. 7 (*below*). *Case 1.* Reëxamination 10 days later shows complete clearing of both lung fields.



The right lung weighed 1010 grams, the left, 885 grams. The lower lobes were not grossly altered, while the upper lobes were firm, relatively dry, and non-crepitant.

Microscopically there was fairly diffuse thickening of the alveolar walls by large numbers of mononuclear cells, collagen in small amounts, and engorged tortuous capillaries. The alveolar exudate was composed of mononuclear cells (many containing hemosiderin), protein precipitate, fibrin clumps covered by a layer of mononuclear cells, and foci of red blood cells. A small number of alveolar capillaries contained hyaline thrombi; small arterial and arteriolar branches of the pulmonary artery frequently exhibited medial thickening, loss of muscle cells, and leukocytic infiltrations. The inner surfaces of some respiratory bronchioles and alveolar ducts were covered by fibrin, and others by eosinophilic non-fibrinous material (not taking the phosphotungstic acid-hematoxylin stain).

Case 2. J. P., a white male, 16 years of age, with a past history of active rheumatic fever in 1935 and 1938, was admitted on December 20, 1943 because of the onset of marked malaise, weakness, dyspnea, and joint pain following a cold two weeks previously.

Physical Examination: Patient appeared severely ill, and was dyspneic and orthopneic. Temperature 102°, pulse 120, and respirations 40. The heart was enlarged, rate rapid, signs of mitral stenosis and insufficiency, and possibly aortic insufficiency as well, were present. The chest was clear, save for questionable signs of fluid at the right base. Liver was not felt. No edema.

Course: On December 21, 1943, chest films revealed clear lung fields (figure 10), but on December 25, dyspnea and orthopnea became much more severe despite digitalization, and cough productive of blood-streaked white sputum appeared. Signs of fluid at both bases and bilateral moist râles appeared during the subsequent course. On January 4, chest roentgenograms demonstrated an extensive bilateral pulmonary infiltration (figure 11). The white blood count, normal on admission, was elevated from December 28 until death. Fever and tachycardia persisted throughout.

Necropsy: There was an ascites of 750 c.c. and a bilateral hydrothorax of 800 c.c. on the right and 400 c.c. on the left. The heart with the adherent pericardium weighed 600 grams; it was hypertrophied and dilated. The chordae of the mitral valve were thickened. There were verrucae on the line of closure of both the mitral and aortic valves. Numerous Aschoff bodies were present in the myocardium. The liver weighed 1,980 grams and exhibited slight evidence of passive congestion.

The lungs weighed 600 grams each and their pleural surfaces were covered by a fibrinous exudate. The cut surface was wet with edema fluid and was variegated in appearance. In focal areas, the alveolar walls were thickened by large numbers of mononuclear cells and a slight increase in collagen. There was an alveolar exudate consisting of large mononuclear phagocytes (at times with foamy cytoplasm), polymorphonuclear leukocytes, red blood cells, protein precipitate, and clumps of fibrin. In a few arterioles the media was thickened and apparently edematous, but no thrombi were seen. The inner surfaces of respiratory bronchioles and alveolar ducts were covered by fibrin strands and also by non-fibrinous material (which neither stained with phosphotungstic acid hematoxylin nor Sudan III). In many foci the exudate within alveoli and respiratory bronchioles was organized to form intraluminal bundles of fibroblasts and collagen, frequently covered by cells resembling epithelium. The interstitial tissues were edematous and also contained foci of fibroblastic proliferation.

FIG. 8 (*above*). *Case 1.* Second attack one year later reveals recurrence of the infiltration, which had again completely resolved on reëxamination ten days later.

FIG. 9 (*below*). *Case 1.* Third attack five years later which terminated fatally within 15 days. Serial reëxaminations until shortly before death showed no change in the infiltration.

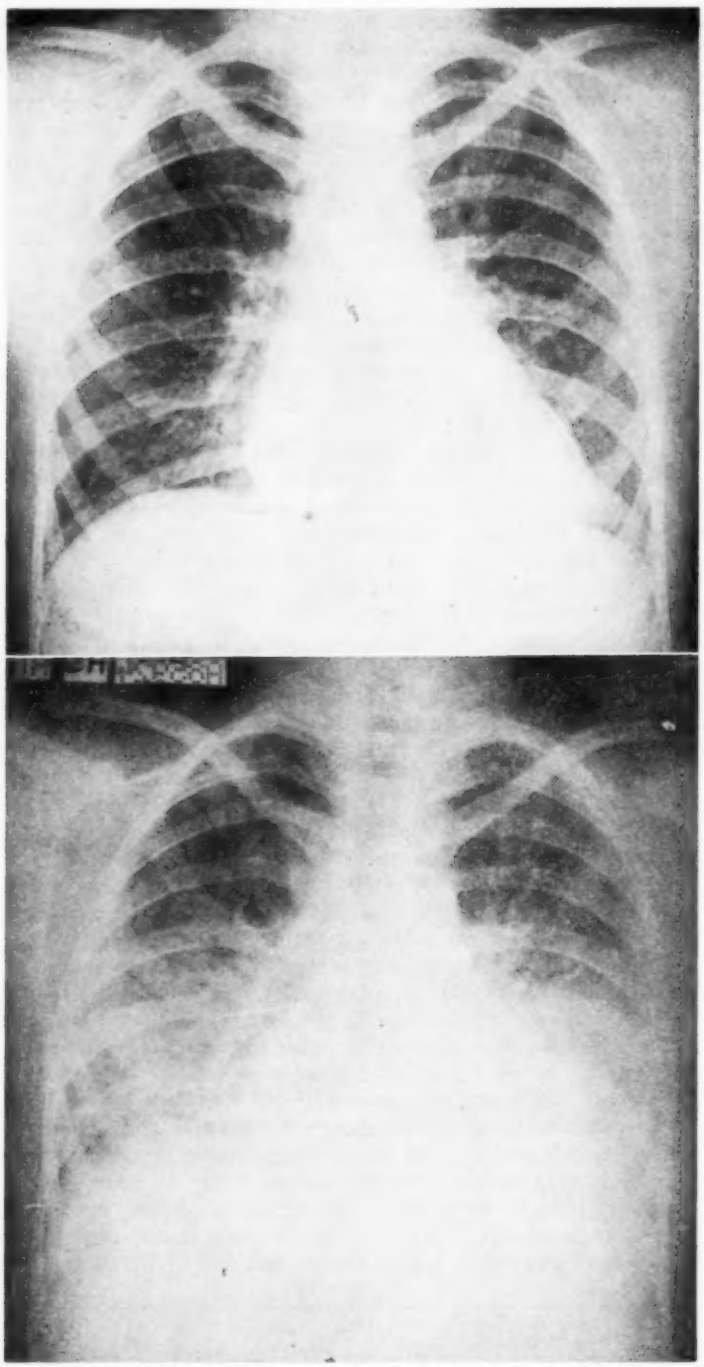


FIG. 10 (*above*). *Case 2.* J. P., age 16, male. Initial chest film before onset of respiratory distress reveals clear lung fields.

FIG. 11 (*below*). *Case 2.* Roentgenogram after development of clinical symptoms, showing a mottled and streaked parenchymal infiltration throughout the lower two-thirds of both lung fields, resembling pulmonary congestion.

Case 3. R. M., a white female, 13 years of age, was admitted to the New Haven Hospital on January 21, 1940 with a past history of "flu" in March, 1939, followed after seven weeks by a migrating arthritis and chorea. A diagnosis of rheumatic heart disease was made and the patient kept in bed for a total of five weeks. She was asymptomatic until three days before admission, when she developed a sore throat with a temperature of 103° F.

Physical Examination: Temperature 102.7°, pulse 30, respirations 20. The significant findings included an enlarged, overactive heart with signs of mitral stenosis and insufficiency, clear lung fields, and no peripheral signs of failure.

Course: Temperature and pulse remained elevated and leukocytosis persisted at about 25,000 throughout hospital stay. On the second day, the patient became profoundly dyspneic, with only a few fine râles at both bases, and was unrelieved by subsequent digitalization. Roentgen-ray examination of chest revealed a picture indistinguishable from pulmonary edema (figure 12). Despite constant oxygen, cyanosis became increasingly severe. Death occurred on the sixth hospital day.

Necropsy: The heart weighed 330 grams and was dilated as well as hypertrophied. The epicardium was covered by fibrinous exudate. The margins of the mitral and aortic valves were thickened and rolled but not stenotic. These valves and the left auricular endocardium contained verrucae. One chorda of the mitral valve had ruptured. Numerous Aschoff bodies were observed in the myocardium. The liver weighed 1215 grams, and was minimally involved by passive congestion.

The right lung weighed 885 and the left, 710 grams. The surfaces were variegated in color with small red areas on a pale pink-gray background.

Microscopically the alveolar walls were diffusely thickened by mononuclear cells and a few fibroblasts with some increase in collagen. The alveolar exudate consisted of large foamy mononuclear phagocytes, much hemorrhage, scattered polymorphonuclear leukocytes, protein precipitate, and fibrin clumps. Many hyaline thrombi were present in alveolar capillaries and arterioles; in some small arterial branches of the pulmonary artery, the media was thick with loss of smooth muscle cells and scattered nuclear fragments. Some alveolar ducts were lined by fibrin and others by a nonfibrous layer of eosinophilic material (not staining with phosphotungstic acid hematoxylin) which stained faintly with Sudan III. The septal tissues were edematous.

Case 4. S. S., a white female, three years of age, was admitted to the New Haven Hospital on February 6, 1946 because of the sudden onset of profound dyspnea and orthopnea, associated with a sore throat, three days before admission. Two days before admission, a dry cough appeared. During the preceding two months, she had suffered recurrent attacks (at least five) of arthritis with fever.

Physical Examination: Child was dyspneic, orthopneic, and appeared gravely ill. Temperature 102°, pulse 180, respirations 40. Heart was slightly enlarged, rate rapid with gallop rhythm and a loud systolic murmur at the apex. Lungs clear. Liver was down two fingers'-breadth in the mid-clavicular line. No edema.

Course: Roentgen-ray examination of the chest on admission revealed an extensive bilateral pulmonary infiltration (figure 13), which persisted essentially unchanged on serial follow-up examinations until four days before death, when, following a clinical flare-up, it spread to involve both lungs almost completely. Leukocytosis, fever, tachycardia and striking dyspnea persisted throughout. Digitalization was ineffectual. On February 12, a few basilar râles were heard for the first time; by February 16 they had cleared. The liver never increased in size; no peripheral edema appeared.

Necropsy: The heart weighed 85 grams and was hypertrophied without significant dilatation. There was no valvular thickening, but verrucae were present along the line of closure of the mitral valve. The myocardium contained a few Aschoff bodies.

The surface of the lungs was light gray-pink, mottled with red-purple areas corresponding to secondary lobules.

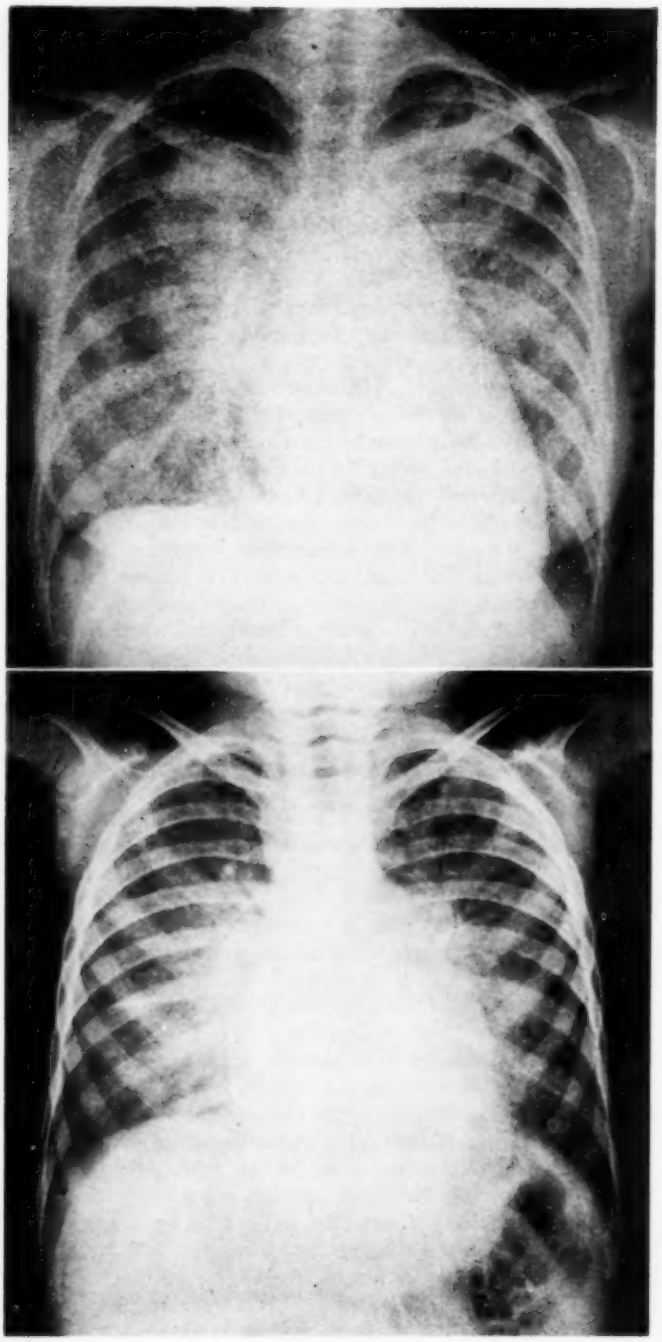


FIG. 12 (*above*). *Case 3.* R. M., age 13, female. Large zones of increased density, with irregular margins, occupy the greater part of both lung fields, assuming a "butterfly" distribution and leaving a peripheral clear zone of emphysema. This appearance is identical with that usually designated as pulmonary edema.

FIG. 13 (*below*). *Case 4.* S. S., age 3, female. Note the bilateral, multilobar, linear and reticular infiltration with a peripheral clear zone. Reëxamination one month later, following a clinical exacerbation, showed almost complete obliteration of aerated lung.

The alveolar walls were thickened by mononuclear cells and the alveolar exudate consisted of large mononuclears, phagocytes, focal hemorrhage, and small masses of fibrin frequently covered by flattened cells; there were rare hyaline thrombi in alveolar capillaries. Some respiratory bronchioles were lined by a thin layer of eosinophilic material which at times was sudanophilic; the lumen of others was completely filled by it.

Case 5. T. J., a white female, 22 years of age, was admitted to the New Haven Hospital on December 8, 1946. She gave a history of chorea at the age of eleven. She had been well until two days before admission, when she developed profuse sweating, high fever, and embolic phenomena in her extremities.

Physical Examination: Patient appeared acutely ill. Temperature 104°, pulse 110, respirations 24. The heart was enlarged, with signs of mitral stenosis, and insufficiency. The lungs were clear. No signs of congestive failure. Several petechiae were present on the sole of the left foot.

Course: A heavily positive blood culture for hemolytic *Staphylococcus aureus* led to the administration of penicillin by constant intravenous drip in doses ranging from 1,000,000 to 500,000 units a day until January 10, when the drug was discontinued. Sixteen consecutive blood cultures were negative but four colonies were found on a final blood culture taken three days before death. Two days after admission, venous pressure and circulation time were done because of the presence of dyspnea. The circulation time was normal (17 sec.) and the venous pressure was

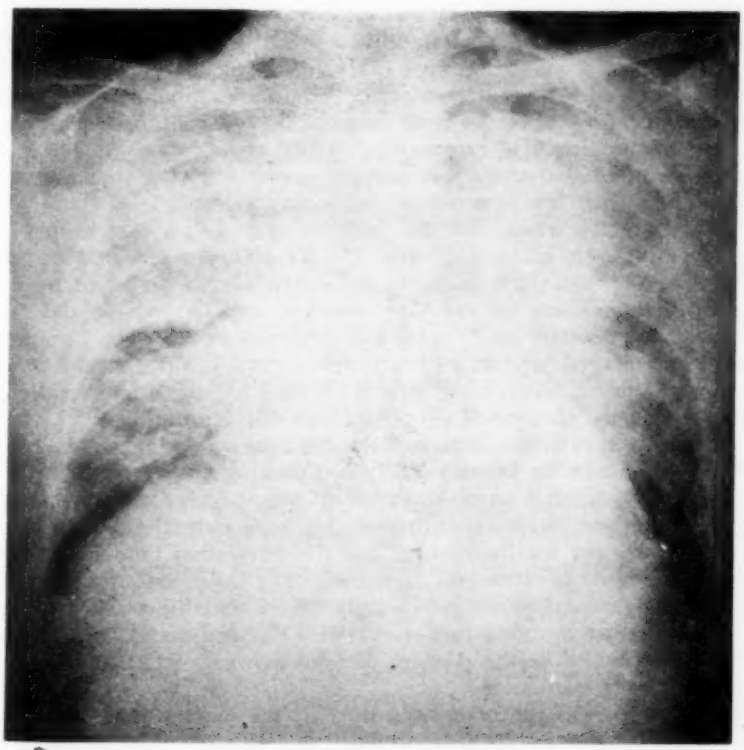


FIG. 14. Chest roentgenogram of a 53 year old male with arteriosclerotic heart disease, taken shortly before death from congestive heart failure, shows the characteristic features of pulmonary edema. Despite its greater extent, note the striking resemblance of this infiltration to figures 9 and 12.

only slightly elevated (13 cm.). No edema or hepatomegaly was present, but there were a few transient basilar râles. Digitalization was instituted without relief. On January 8 the patient developed a left pleurisy; the temperature, which had hovered around 100 to 101°, rose to 102 to 104°; the white blood count, normal previously, rose to 17,000. Roentgen-ray examination on January 10 revealed a fan-like linear infiltration radiating out from both hilar regions, tending to be lost in a more homogeneous density in the lower lobes—a pattern indistinguishable from cardiac failure. The development of a pneumonia in the face of 500,000 units of penicillin per day, with the peculiar roentgen-ray features mentioned, suggested a non-bacterial etiology. On February 9, patient began to cough up blood-tinged sputum. Reëxamination of the chest at that time revealed some increase in the infiltration previously noted. Despite increasing dyspnea, venous pressure and circulation time were normal on February 12. Chest signs were minimal to absent, except terminally.

Necropsy: There was a bilateral hydrothorax with 500 and 300 c.c. on the right and left, respectively. The heart was hypertrophied, weighing 310 grams. The mitral valve, which was scarred, contained two friable vegetations, and a similar one was present on the aortic valve; no bacteria were present on culture or microscopic section. Aschoff bodies were numerous in the myocardium. Infarcts were present in the spleen and left kidney. The liver weighed 1,435 grams and exhibited slight passive congestion.

The left lung weighed 710 grams and the right, 740 grams. They were noncrepitant, firm, and mottled dark-red and gray-pink.

The alveolar walls were diffusely thickened by mononuclear cells. The alveolar exudate consisted of large mononuclear cells, scattered polymorphonuclear leukocytes, focal hemorrhage, and protein precipitate. Hyaline thrombi were present in alveolar capillaries and arterioles. Some respiratory bronchioles and alveolar ducts were lined by fibrin, others by a non-fibrinous eosinophilic and sudanophilic substance not stained by phosphotungstic acid hematoxylin; septal edema was present.

It should be noted that there was nothing suggestive of a suppurative process such as would be seen in a staphylococcal pulmonary infection.

Case 6. S. deM., a white male, 16 years of age, with a past history of acute rheumatic fever in 1941, was admitted to the New Haven Hospital on December 29, 1945 because of progressive weakness and cough over a period of five weeks.

Physical Examination: Patient was dyspneic and orthopneic, and appeared chronically ill. Temperature 103°, pulse 110, respirations 30. The significant findings included an enlarged, overactive heart with signs of mitral stenosis and insufficiency and aortic insufficiency, clear lung fields save for a few moist râles over the left lower lobe, and the absence of peripheral signs of failure.

Course: Roentgen-ray examination of the chest on admission revealed clear lung fields; repeat examination on January 30, 1946, following an exacerbation of dyspnea two days previously, showed an accentuation of the vascular structures throughout both lung fields without evidence of intervening parenchymal infiltration. At this time the venous pressure was borderline, and the circulation time slightly elevated; shortly thereafter, peripheral edema appeared. Digitalization afforded no relief. Tachycardia and dyspnea became increasingly severe and the production of blood-streaked sputum, noted on admission, recurred. Physical signs in the chest were slight until shortly before death. Patient died on February 11, 1946, about one and one-half months after admission.

Necropsy: There was subcutaneous edema of the legs, sacrum, and face. The heart, weighing 600 grams, was hypertrophied and dilated. The mitral and aortic valves were thickened, but not stenotic, and contained verrucae on the line of closure. There were many Aschoff bodies in the myocardium. The liver weighed 1435 grams and showed passive congestion.

The right lung weighed 1200 grams and the left 800 grams. There were small infarcts in the anterior margins of the right upper and left lower lobes, with a fibrinous pleural exudate overlying and surrounding each. The surface was mottled, light pink and dark red.

In focal areas the alveolar walls were thickened by increased numbers of mononuclear cells and fibroblasts. The alveolar exudate consisted of mononuclear phagocytes, foci of hemorrhage, precipitated protein, and fibrin strands. A few hyaline thrombi were present in the alveolar capillaries and arterioles, and there was loss of smooth muscle cells with scattered nuclear fragments in the walls of arteries; some respiratory bronchioles were lined by fibrin, others by a non-fibrinous eosinophilic and sudanophilic membrane not stained by phosphotungstic acid hematoxylin. The intra-luminal exudate in alveoli and respiratory bronchioles was organized by tuft-like masses of fibroblasts and collagen, covered by flattened epithelial-like cells; there was also interstitial fibroblastic organization.

Clinical and Roentgenologic Features

The principal findings in the six verified examples of rheumatic pneumonia are summarized in tables 1 and 2. All cases exhibited clinical, laboratory, and anatomical evidence of active rheumatic carditis. In contrast to the experience of Masson et al.[18] five of the cases were beyond the

Table I

Summarized History of Cases of Rheumatic Pneumonia

Name[1]	Age	Sex	Prev. Attacks of Active R.F.	Onset of R.F. to Onset of Pneum.	Rapidity of Onset	Chill	Hacking Cough	Dyspnea	Pleurisy
A. G.[c]	29	F	3	3½ mos.	xxxx	0	x	xxxx	x
J. P.	16	M	2	16 days	xxxx	0	x	xxxx	x
R. M.[2]	13	F	1	4 days	xx	0	x	xxx	0
S. S.	3	F	0	2 mos.	xxxx	0	x	xxxx	0
T. J.	22	F	1	1 mo.	xxx	x[2]	x	xx–xxxx	x
S. deM.	16	M	1	10 weeks	xxx	0	x	xxx	0
A. G.[a]	23	F	1	8 mos.	xxx	0	x	xxx	x
A. G.[b]	25	F	2	12 mos.	xxx	0	x	xxxx	0

[a, b, c] Represents three attacks of rheumatic pneumonia in one patient.
[1] All cases had active carditis and were in cardiac failure.
[2] Only case with pericarditis.
[3] Had staphylococcal endocarditis and septicemia.

first decade of life and two were in the third decade. Two of the six cases were males. Five had had previous attacks of active rheumatic fever. In one case (A. G.), three recurrent attacks of rheumatic pneumonia, the last terminating fatally, punctuated a low-grade subacute rheumatic fever. Pericarditis occurred in only one (R. M.) The pneumonic manifestations may develop almost simultaneously with the onset of a fulminating, acute rheumatic fever (R. M.), or light up a smouldering subacute rheumatic fever that has gone on for weeks or months.

Mode of Onset: A striking feature has been the abrupt onset, in the space of hours, of profound respiratory distress.

TABLE II

Summarized Findings and Course of Cases of Rheumatic Pneumonia

Name	Temperature		Sputum Amt.	Type[1]	Phys. Signs	No. of Lobes Involved	White Bl. Count		Sputum, Throat Cultures	Course	Result
	Adm.	Later					Total	% Pmn's			
A. G.[a]	104.8	101–2	x	MB	0–x	5	22.0	80–90	0	15d	D
J. P.	102	102–3	x	MB	xxx	4	16.0	78	0	12d	D
R. M.	102.7	102–3	0	0	x	5	25.0	85	0	5d	D
S. S.	102	100–102	0	0	0–x	5	14.5	80	0	31d	D
[2]T. J.	105	100–102	x	MB	0–x	5	5.0–18	90	x	40d	D
S. deM.	101	98–100	x	MB[1]	x–xx	5	9.0	75	0	12d	D
A. G.[a]	101.4	98.6	x	MB	x	3–5	18.0	75	0	8d	L
[2]A. G.[b]	103	101–98.6	x	MB	xx	5	26.0	93	x	7d	L

[a, b, c] Represents three attacks in one patient.
[1] M mucoid.
B blood streaked.
B[1] diffusely bloody.
[2] No response to sulfapyridine.
[3] Patient had acute staphylococcal endocarditis; septicemia, but not pneumonia responded to penicillin.

Dyspnea, Orthopnea, and Cyanosis: This triad was a constant manifestation of the disease, far overshadowing all other symptoms. Respirations were rapid and moderately deep, and all patients required oxygen.

Cough and Sputum: A dry, hacking cough, occasionally productive of small amounts of white, mucoid sputum which was usually streaked with blood was present in all cases. At times the sputum became grossly bloody, but the "rusty" sputum of pneumococcal pneumonia was never seen. In no case was purulent sputum observed.

Pleurisy: Pleuritic pain of fleeting nature was inconstantly present. It occurred either as a prodromal manifestation or appeared during the course of the disease, but in no instance was it a dramatic initial symptom as in lobar pneumonia.

Fever: The temperature was moderately to markedly elevated, ranging from 100° to 105° F. Whether this is a reflection of the severity of the systemic rheumatic infection, as Gouley maintains, or is directly attributable to the pulmonary complication, is not clear.

Physical Signs: In contrast to the striking air hunger, the physical signs in the lung were surprisingly few. In one case (A. G.[a]) the lungs were completely clear to physical examination throughout the course despite roentgen evidence of a diffuse infiltration involving all five lobes. Another case (S. S.) with profound dyspnea and roentgen evidence of equally extensive infiltration was similarly devoid of physical signs except for transient fine basilar râles about one week after admission and again terminally. This dichotomy between the paucity of physical signs and the profundity of respiratory distress was noted to a variable extent in all cases. In only one case (J. P.) were physical signs in the chest considered prominent, and at autopsy a large bilateral pleural effusion was found.

Cardiac Failure: Despite the fact that some degree of cardiac failure was present in all cases, there were few physical signs in the lung which were attributable to it. The possibility that pulmonary signs of decompensation might mask the otherwise "silent" character of the pneumonic process must, however, be kept in mind. There was failure to respond to digitalis in every case, as might well be expected in the presence of active carditis.

Laboratory Data: The *white blood cell count* was elevated in all cases ranging from 14 to 26 thousand. *Differential counts* revealed a polymorphonuclear leukocytosis of from 75 per cent to 93 per cent of the total count. There was no anemia except in the case (T. J.) with a complicating staphylococcal septicemia.

Despite the presence of active rheumatic fever throughout the series, only one sputum culture was positive for β-hemolytic streptococci, although both sputum and throat cultures were repeatedly taken. No pathogenic pneumococci (by mouse inoculation and typing) were found.

Roentgen Findings: The roentgen appearance of rheumatic pneumonia is indistinguishable from that usually associated with cardiac failure. The significance of the pulmonary roentgen findings in rheumatic heart disease with and without decompensation has yet to be elucidated. Hence, differentiation between changes ascribable to such an inflammatory process and those secondary to purely cardiodynamic factors, on the basis of roentgen-ray features alone, is impossible. For convenience, the pulmonary roentgen changes associated with rheumatic heart disease will be grouped under three categories: *

(1) *Vascular engorgement:* by this term is meant an increased prominence of the pulmonary arterial shadows throughout both lung fields. The precise relationship of this finding to cardiac failure is obscure.

(2) *Pulmonary congestion:* by this term is meant a roentgen appearance characterized by the presence of coarse, fuzzy, arborizing linear shadows, radiating out from the hilar regions and presumably vascular, whose irregular margins merge gradually with the adjacent aerated lung parenchyma. Although such an appearance in itself is nonspecific, in association with cardiac enlargement and/or suitable clinical data it is usually attributable to cardiac failure.

(3) *Pulmonary edema:* by this term is meant a roentgenographic appearance characterized by a diffuse, moderately dense, fluffy or hazy parenchymal infiltration which is usually bilateral, multilobar, and often assumes a "butterfly" distribution, with a peripheral clear zone of emphysema, and with varying degrees of obliteration of individual vascular shadows. Cardiac failure is usually present with this condition but is probably not causally related to it. Luisada [17] has summarized the evidence for this view.

It should be recognized that these terms, as used here, refer only to ob-

* This classification should not be construed as all-inclusive since other pulmonary changes occur in association with rheumatic fever which are not subsumed under any of these categories.

jective roentgen findings and do not imply cardiac failure as à causal factor. This point deserves emphasis inasmuch as identical roentgen changes have been present in pathologically verified cases of rheumatic pneumonia.

The cases studied exhibited each of the three appearances described above, though pulmonary edema was the most common. In the presence of suitable clinical data, a roentgen appearance characterized by widespread, bilateral, multilobar, non-segmental infiltration should suggest the diagnosis of rheumatic pneumonia and aid in its differentiation from bacterial and primary atypical pneumonic consolidations.

Course and Prognosis: In view of the fatal outcome of all cases in this series, the disease appears to have a grave prognostic significance. Death occurred within 5 to 40 days of the onset of this complication. It should be noted, however, that one case (A. G.) survived two probable attacks before succumbing to the third. In these two non-fatal attacks, roentgen-ray evidence of complete resolution was present within 10 days, although it may have occurred sooner.

Response to Treatment: Salicylates did not alter the course of the disease. Penicillin, administered as a constant intravenous drip of 500,000 to 1,000,000 units per day over a period of several weeks, did not prevent its development in one case (T. J.). In one of the non-fatal attacks (A. G.[b]), resolution did not appear causally related to the administration of sulfapyridine.

Differential Diagnosis: There is little difficulty in distinguishing rheumatic pneumonia, in the form here encountered, from bacterial or primary atypical pneumonias. The mode of onset, character of the sputum, paucity of physical signs, and absence of pathogenic organisms in the sputum, together with roentgen findings of a diffuse, bilateral, non-segmental infiltration, all combine to exclude a diagnosis of bacterial or primary atypical pneumonia.

It is apparent that the main problem consists in distinguishing rheumatic pneumonia from various stages of cardiac failure. This is impossible by roentgen-ray examination alone. Certain clinical features, however, aid in making a differential diagnosis. On the basis of the cases reported here and those described in the literature, the absence of an active carditis makes the diagnosis of rheumatic pneumonia untenable. Where cardiac decompensation is not present, as reported by Coburn, the roentgen-ray features assume added significance. In the presence of a widespread pulmonary infiltration, associated pleural pain would suggest an inflammatory rather than a purely congestive origin. An abrupt onset of profound dyspnea without commensurate physical signs would also favor the diagnosis of rheumatic pneumonia. The principal differential features are summarized in table 3.

Roentgen Incidence of Pulmonary Complications of Acute Rheumatic Fever: In an attempt to evaluate the roentgenographic incidence and nature of pleuro-pulmonary complications of active rheumatic fever a series of 100

TABLE III
Differential Diagnosis

	Acute Pul. Edema	Rheum. Pneumonia	Bact. Pneumonia
Presence of active carditis	Not necessarily	Always	Rare
Fever	Normal-mod.	High	High
Pleuritic pain	Absent	Frequent	Frequent
Dyspnea	Profound	Profound	Commensurate with physical signs
Sputum	Pink, frothy	Mucoid, blood-streaked	Purulent
Physical findings	Marked	Few	Moderate to marked
X-Ray			
Distrib.	Non-segmental	Non-segmental	Segmental or lobar
No. lobes	Multiple, bilateral	Multiple, bilateral	Rarely more than 2 or 3 lobes
Type of lesion	Soft, hazy, patchy infiltration	Soft, hazy, patchy infiltration, or linear and reticular radiation from hilar regions	Dense, homogeneous consolidation
Pathogens in sputum	None	Usually absent	Present

admissions of 91 patients with active rheumatic fever was studied. The results of this study are presented in table 4. Bacterial pneumonia appears to be a rare complication of active rheumatic fever, since it occurred in only two of 100 attacks in the present series; both of these were cases of pneumonitis on a bronchiectatic basis, and no instance of lobar or primary atypical pneumonia was encountered. Such a low statistical incidence of intercurrent pneumonias facilitates the differential diagnosis of rheumatic pneumonia.

TABLE IV
Roentgen-Ray Findings in Clinical Types of Rheumatic Fever—100 Attacks in 91 Cases

	Arthritis Alone, 13 Attacks	Carditis without Decompensation, 66 Attacks	Carditis with Decompensation, 21 Attacks
Vasc. Engorgement and Pulm. Congestion	0	6	21[a]
Pleural Effusion	0	9[b]	7[c]
Atelectasis	0	3	1
Bact. Pneumonia	0	2	0
Pulm. Infarct	0	0	2
Rheum. Pneumonia	0	0	6
Totals	0	20	37

[a] In two cases engorgement was questionable as vessels were obscured by rheumatic pneumonia.
[b] Eight patients had pleuritic pain.
[c] Four patients had pleuritic pain.

The most common pulmonary lesions noted, occurring in 27 per cent of the attacks, were vascular engorgement and pulmonary congestion usually associated with cardiac failure. In a few instances, infiltrations resembling vascular engorgement were not accompanied by clinical evidence of cardiac decompensation. The possibility that these infiltrations represented mild,

non-fatal instances of rheumatic pneumonia was considered, but their symptomatology was not that of the proved cases. In the hospital material studied, the incidence of rheumatic pneumonia was 5 per cent.

Discussion

It is difficult to resolve the discrepancy between the grave clinical picture encountered in these cases (and in those reported by Ravenna, Coburn, and Debré et al.), and the milder syndrome described by Rabinowitz and others. Inasmuch as the two groups were morphologically identical at autopsy, the latter form of the lesion cannot be dismissed as representing an erroneous diagnosis. Despite careful search, however, no instances of "fleeting pneumonitis" compatible with the published descriptions of this mild variant were encountered in the hospitalized cases studied. Inasmuch as the clinical and roentgenological criteria for the diagnosis of rheumatic pneumonia are still inconclusive, the necessity for postmortem verification introduces a possible error in the evaluation of the course and prognosis of the disease by excluding mild cases. Accordingly, the clinical and roentgenological features which are observed in fatal cases need not be expected in more benign instances. The clinical nature of such mild episodes must await the opportunity to observe and study adequate numbers of them in which autopsy verification is possible owing to death from accidental or unrelated causes.

It is probable that gradations in the pathological extent and severity of the disease would be reflected in the prognosis and clinical syndrome. However, any simple and direct correlation between individual clinical symptoms and the anatomical lesions is only speculative at this time. In contrast to the lungs of acute pulmonary edema, the sectional pulmonary surfaces in rheumatic pneumonia, though appearing moist, fail to exude frothy, serosanguinous fluid. This absence of a thin, liquid exudate may explain the striking absence of râles in the latter condition, while the peripheral zone of emphysema so clearly brought out by roentgen examination may be related to the absence of dullness to percussion or changes in tactile fremitus. The profound dyspnea which characterized the severe cases encountered in the study can be considered either a cause (as Farber and Wilson have indicated) or an effect of the deposition of hyaline pseudomembranes in the terminal bronchioles and alveolar ducts, with consequent atelectasis of multiple tributary alveoli. Epstein and Greenspan have suggested that dyspnea due to associated cardiac decompensation is necessary for the conversion of the intraluminal exudate into these hyaline pseudomembranes. On this basis, however, cardiac failure becomes an integral and necessary component of the disease. Such a conclusion is at variance with Coburn's observation of a verified case in which no evidence of decompensation was present, and with the minimal degrees of decompensation in two of the six cases reported here. There can be no doubt that an active rheumatic carditis with at least some degree of failure is almost always associated with

rheumatic pneumonia, but the available evidence does not permit any conclusions concerning the causal relationship between the two conditions.

Despite their distinctly different pathologic character, pulmonary edema and rheumatic pneumonia share a common, or at least closely similar, roentgen appearance. This fact, together with the non-segmental, multilobar distribution, suggests that the pathogenesis of rheumatic pneumonia is based upon a diffuse pulmonary vascular lesion, to which the exudate, pseudomembranes, and cellular infiltration are secondary. This inference is supported by the histological studies of cases of varied duration reported by Epstein and Greenspan and by Gouley. It is possible that further evidence concerning the evolution of the disease will result from careful study of serial chest roentgenograms in patients with severe acute rheumatic fever.

Summary and Conclusions

1. Six cases of active rheumatic fever with carditis, presenting the characteristic pathological features of rheumatic pneumonia, have been studied. A uniform clinical picture was encountered, characterized by an abrupt onset of profound respiratory distress in the absence of commensurate physical signs in the chest. Hacking cough with scanty, blood-streaked sputum, moderate to high fever, and leukocytosis were also present. The disease was manifested roentgenologically by a bilateral, multilobar, non-segmental infiltration which resembles pulmonary edema.

2. The clinical and roentgenological features of rheumatic pneumonia were observed in five of 100 attacks of active rheumatic fever occurring in 91 patients. No instance of lobar or primary atypical pneumonia was encountered in this series, and pneumonitis secondary to bronchiectasis was found only twice. Rheumatic pneumonias therefore appear to be more frequent than intercurrent pneumonias during the course of active rheumatic fever.

3. All cases of rheumatic pneumonia observed in this study terminated fatally. Therefore, this manifestation of rheumatic fever would appear to carry a grave prognostic significance.

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BRONCHIAL SPASM IN CARDIAC ASTHMA *

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The object of the experiments to be reported here was to elucidate some of the problems associated with the dyspnea of heart disease. Specifically, we wanted to learn something of the mechanism of the wheezing sometimes found in heart disease, to study the vital capacity in this type of heart failure and in that associated with basal râles, to study the effect of venesection on the vital capacity in such cases and to study as far as possible the expiration time and the velocity of expiration in heart disease.

The fact that cardiac asthma may simulate bronchial asthma closely has of course been known by clinicians for hundreds of years. Until quite recently the examining physician had consciously or unconsciously, when confronted with wheezing respiration, used the presence or absence of moist râles at the bases of the lungs as an important criterion for the differential diagnosis. In other words, if he heard sibilant râles scattered throughout both lungs with moist râles at one or both bases, he classified the case as one of cardiac asthma. However, if he heard wheezing râles diffusely scattered throughout the chest without basal râles, he usually made the diagnosis of bronchial or allergic asthma.

In 1939, studies from this department [1] showed that this concept was erroneous for several reasons. Most important of all, it was demonstrated at that time that wheezing might occur in cardiac asthma without the presence of basal râles and that this wheezing was entirely indistinguishable from the point of view of physical signs from the râles of bronchial asthma. Furthermore, it was shown that some cases of true allergic asthma were complicated by moist râles at the bases. We also showed by means of studies of the velocity of the circulation that estimation of the circulation time could be used to distinguish, in the great majority of cases, cardiac from bronchial asthma.

Soon thereafter it was found that the then currently held idea that cardiac and bronchial asthma could be differentiated from each other by the response to adrenalin was mistaken. Most cases of cardiac asthma, especially if they were of the type that had wheezing respirations, a type which we designated as "asthmatoid heart failure," were relieved promptly by the administration of adrenalin. We felt therefore that if the mechanism of the dyspnea and its relief by adrenalin were better understood, much light could be thrown on the entire subject of the differential diagnosis. It was with this in mind that the present study was undertaken.

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It is not difficult for most of us to understand the reasons for the decrease in vital capacity when moist râles are present in the lung bases. As shown diagrammatically in figure 1, No. 2, free edema fluid is present in the alveolar spaces. Basal râles are heard in such cases and if there is enough fluid to rattle around in the bronchi, the familiar signs of pulmonary edema are

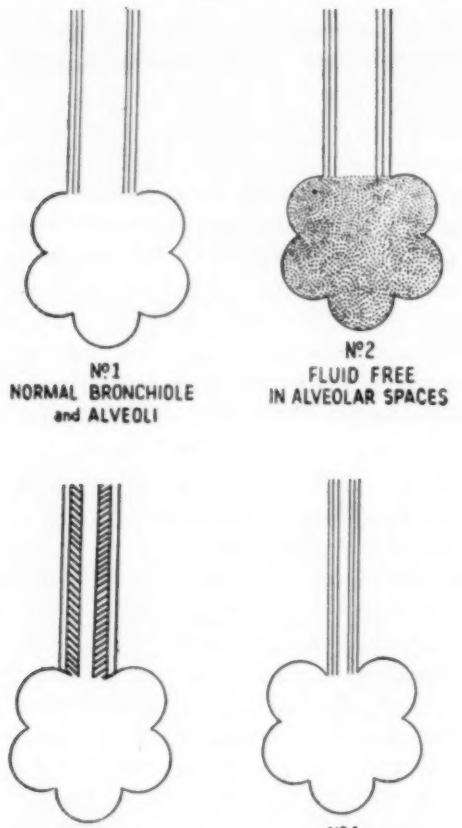

FIG. 1. Diagrams to illustrate genesis of cardiac asthma.

heard. It is somewhat more difficult to understand how heart failure leads to wheezing respirations without moist râles. A possible mechanism, analogous to that occurring in bronchial asthma, is shown in figure 1, No. 3 which schematically shows encroachment on the lumen of the smaller bronchioles by severe edema and engorgement of the submucosa. At the time that our first paper on asthmatoid heart failure was published, we thought that this was probably the dominant mechanism. Since then, however, we have given a great deal of thought to the possibility that bronchial spasm, on a reflex basis, might be the principal factor (figure 1, No. 4).

Patients with heart failure were studied in several groups in the wards of the Kings County Hospital, the Goldwater Memorial Hospital and in the

cardiac station of the Bushwick Hospital. The first group was constituted of cases with sibilant râles alone but no evidence of basal râles (table 1). There were nine such cases all of which had heart failure as evidenced by other physical signs and especially by a marked prolongation of the circulation time. There was only one case of rheumatic heart disease, five cases of hypertensive heart disease and three with coronary heart disease and myofibrosis cordis. Vital capacity studies were done with these patients in as nearly basal conditions as possible. Two tests were taken not less than

TABLE I

Heart Disease: "Asthma": No Basal Râles

Age	Vital Capacity	Increase After Adrenalin
51	2.1	450
52	2.4	510
61	1.6	400
45	1.9	325
23	2.3	520
49	2.7	400
55	1.2	225
56	2.3	425
56	1.9	470
Average	Average	Average
49	2.15	425

five minutes apart and, as is usual in such cases, the second test almost invariably gave the higher figure. In each case the expiration time was noted and the expiration velocity in terms of c.c. per second was charted. The vital capacity in each case was found to be sharply reduced below the calculated normal estimated by the method of Edward and Wilson. The expiration time was the same as that found in normal individuals but the expiration velocity was also markedly decreased.

One-half c.c. of adrenalin was injected subcutaneously in each of these patients and vital capacity studies were taken anywhere from 30 to 90 seconds later and four to five minutes after that. In each case there was a sharp increase in the vital capacity over the reading previously obtained. This increase averaged about 510 c.c.. In five cases inhalations of vaponephrin were used and the results were entirely comparable, an increase in vital capacity taking place almost immediately. The patients almost all felt much improved and no untoward effects were noted although the experiments were started with misgivings.

A control group was used, of 11 cases (table 2), in whom there was marked cardiac failure with basal râles but without wheezing. The vital capacity was even lower than in the previous group, a finding which was not surprising in view of the fact that these cases almost all represented a more advanced stage of failure. Adrenalin or vaponephrin was administered to each of these patients with little or no increase in the vital capacity. Seven patients showed increases of less than 50 c.c. and four patients showed increases of less than 100. In no case was there an increase of more than 100 c.c.

TABLE II

Heart Failure: No Wheezing: Basal Râles

Age	Vital Capacity	Increase After Adrenalin
50	1.4	75
22	2.0	120
61	1.6	50
49	1.5	50
72	1.3	75
71	0.9	105
45	2.1	75
51	1.4	0
62	1.7	25
60	1.2	100
43	1.3	55
Average 53	Average 1.4	Average 59

Four of the patients from the first group were observed several months later at which time they had passed into the second group. These were patients that had started with asthmatic breathing entirely resembling that of bronchial asthma, a stage followed several months later by frank cardiac failure in which numerous râles were heard at both bases. In these cases, a further reduction in the vital capacity was noted to have occurred as the disease progressed and there was little or no response to the administration of adrenalin.

Five normal individuals were used as controls. These were patients with no cardiac or pulmonary disease in whom the vital capacity was 4.5 liters or over. The administration of adrenalin produced no change in the vital capacity.

Several other measurements were taken on the same patients. The expiratory time was taken in most of the subjects. This is the minimum duration of the maximum expiration. The subject is told to exhale as rapidly as possible after completing his deep inspiration and the time is carefully clocked. The expiratory velocity was estimated in terms of c.c. per second. A third measurement, the expiratory pressure, in terms of millimeters of mercury was measured in most of the subjects. The cuff connection of a mercury sphygmomanometer was attached to a rubber tube 50 centimeters long identical with that used in the spirometer. The subject inhaled as deeply as possible and then exhaled forcibly into the manometer in about the same way as for the vital capacity test.

Our results were in agreement with those reported by Desiderio Gross[2] in 1943 with respect to normal individuals. The expiratory time averaged 3.5 seconds and the expiratory velocity about 1360 c.c. per second. The expiratory pressure averaged 122 millimeters of mercury. All of these figures are in close agreement with those obtained by Gross. However, the expiratory time was found to be prolonged in all patients suffering from dyspnea, with or without wheezing respirations. All had expiratory times of 4.0 seconds or higher. Naturally the expiratory velocity was considerably decreased in all cases. Gross, on the other hand, found that the

expiratory time was normal in patients with decompensated heart disease. The expiratory pressure we found, as did Gross, to be markedly decreased in all cases of heart failure with pulmonary symptoms. It was less than half that of normal individuals and averaged 63 millimeters of mercury.

Observations were also made on the effects of phlebotomy on the vital capacity of both normal and cardiac subjects. These results will be reported elsewhere. Suffice it to say that our results merely confirmed the observations of Budelmann [3] that the vital capacity is increased by venesection in patients with cardiac failure and those of Glaser and Macmichael [4] that a similar increase is found in normal individuals.

Several explanations of the increase in vital capacity after adrenalin in our subjects with wheezing respiration are possible and I do not see how, in the light of the information available at present, one can make a final decision. It is possible, of course, that the adrenalin may act by increasing the efficiency of heart action or by decreasing submucosal edema or by relieving congestion in the inter-alveolar framework. I am not inclined to believe that any of these explanations is correct. It seems to me that the speed with which the reactions took place, namely, as rapidly as they could be measured, i.e., within 30 seconds, and the extent of the increase in vital capacity, that relief of spasm of the smaller bronchioles is the most likely explanation.

Summary

1. Bronchial spasm is an important element in certain types of heart failure.

2. Cardiac asthma may occur with asthmatic wheezing and without basal râles. Such cases are indistinguishable by means of physical signs from bronchial allergic asthma and may, as in the case of the latter, be improved by the use of adrenalin.

3. In normal individuals, the administration of adrenalin does not increase the vital capacity.

4. In patients with cardiac failure without basal râles but with wheezing respiration, the administration of adrenalin increases the vital capacity sharply.

5. The vital capacity is not increased by adrenalin in patients with basal râles.

6. The expiratory pressure is sharply decreased in patients with pulmonary congestion or wheezing respiration and the expiratory time is prolonged.

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THE USE OF METHYL-ISO-OCTENYLAMINE IN MIGRAINE *

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THE mechanism by which headache is produced in the migrainous patient is not entirely understood but it almost certainly is a vascular phenomenon dependent upon alterations in caliber of the cerebral, dural, or scalp vessels. Those drugs which most commonly relieve the pain are sympathicomimetic and vasoconstrictor in their action. Of these the one which has best stood the test of time is ergotamine tartrate (Gynergen, Sandoz), but there are certain disadvantages to the use of this material. Aside from dangers of ergotism from prolonged administration, there are frequently unpleasant symptoms such as nausea, vomiting, paresthesias in the hands, and sensitivity to temperature change. In addition migraine headache tends to occur most frequently just before the onset of the menstrual flow and the administration of ergot at that time is frequently accompanied by distressing dysmenorrhea. Many of these unpleasant side effects are less common when the newer ergot derivative, D. H. E. 45 (Dihydroergotamine, Sandoz), is used. Generally speaking, this material, the use of which was first described by Horton,[1] is probably the most universally satisfactory agent for the relief of migraine headache now available.

However, in a desire to avoid the use of ergot in any form in patients who suffer from frequent episodes of migraine headache, other drugs having a similar action have been studied. Of these, methyl-iso-octenylamine † has proved most useful. This material was originally introduced as an antispasmodic drug and has been used most widely in the urologic field. It apparently has a twofold action: namely, mild stimulation of the sympathetic nervous system plus direct relaxation of involuntary muscles and constriction of the blood vessels. We have administered it hypodermically in doses of 100 to 200 mg. to 18 different patients suffering from headaches which fit the general "migrainous" pattern. All of these patients suffered from recurrent unilateral headache, usually beginning early in the morning, accompanied by nausea with or without vomiting. In all of them there is a familial history of similar headaches. All but two of the patients were women.

Once the diagnosis of migraine has been established a test dose (50 to 75 mg.) of Octin should be given with the patient under close supervision. The drug should not be given to patients with hypertension, but fortunately the blood pressure in most patients with migraine tends to be low. A few patients with unstable vasomotor systems do respond with an excessive hypertension to the injection of Octin. This hypertension develops within 10 to

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† "Octin," manufactured by the Bilhuber-Knoll Corporation, of Orange, N. J., who kindly supplied the material for this investigation.

30 minutes after the injection and may persist for three to four hours. If the patient does not respond with an excessive degree of hypertension to this small dose, she is then instructed to administer such an injection to herself as soon as the headache begins to appear. Approximately half of the patients so treated will achieve prompt and dramatic relief of the pain, frequently within 10 to 15 minutes after the injection. So far we have been unable to predict in advance either from history or physical examination which patients will obtain relief and which ones will not. When relief is obtained it usually can be reproduced with subsequent headaches. The dose necessary to produce relief varies among different patients between 100 and 200 mg. The oral administration of 130 to 200 mg. of Octin mucate has occasionally been helpful.[2]

It should be reëmphasized that the individual response to this drug varied tremendously. We have seen no serious untoward effects from the 100 mg. dose, but the larger doses occasionally produce palpitation, hypertension, dizziness, and even syncope. The occasional patient who requires relief from headaches two or three times weekly may develop a general increase in "nervous tension" and palpitation, but this can usually be controlled by small doses of sedatives. One patient under our management has received 113 injections of Octin in doses of 150 to 200 mg. during a period of 15 months. She has shown no toxic symptoms aside from slight nervousness, and relief of the headache continues to be prompt and complete. She has at no time developed hypertension subsequent to the injections. On the other hand, several patients have had rises in blood pressure from a normal of 100 mm. of Hg systolic and 70 diastolic to as high as 185 systolic and 110 diastolic within 30 minutes after the injection of 150 mg. We do not recommend the use of the drug in patients who respond in this way.

Toxicity experiments on animals have been carried out by Drs. R. P. Walton and C. B. Preacher [3] and have not shown any appreciable deleterious effect.

It is obvious, therefore, that this drug is not suitable for the treatment of all patients suffering from migraine headache. However, in those patients in whom it produces prompt relief and in whom it does not produce any hypertensive effect, its superiority over other drugs so far employed for the symptomatic relief of this condition is considerable. It does not produce nausea and vomiting, nor does it cause peripheral vasoconstriction in the hands, which occasionally is annoying in patients treated with ergot. When used with caution and careful control in properly selected patients it offers significant advantages in the symptomatic control of migraine.

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BRUCELLA SENSITIZATION: A CLINICAL EVALUATION *

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In a recent paper dealing with the laboratory diagnosis of undulant fever, Lee Foshay,[9] when discussing the chronic types of the infection, made the following significant statement: ". . . We must expect many current diagnostic errors due to imperfect understanding of the clinical aspects of the disease, to imperfections in our laboratory tests, to misuse of these tests and to misinterpretation of their results."

A comprehensive review of the literature as it pertains to chronic brucellosis,[2, 4, 6, 7, 14, 15, 17, 18, 19, 25, 27, 29, 30, 31, 37] while impressive as to evidence favoring the frequent occurrence of a low grade, chronic form of the infection, makes one feel that there is much truth in Foshay's statement and leaves one with a strong desire for a better understanding of the disease. From the clinical standpoint—that is of proved chronic cases—two facts are impressive: the subjective findings are conspicuous because of their multiplicity and variability; the objective findings are conspicuous because of their absence. Such being the case, the desirability for reliable laboratory diagnostic criteria at once becomes apparent. While the tests in vogue may each have a sphere of usefulness, many imperfections and limitations complicate their indiscriminate use.[1, 3, 8, 9, 17, 20, 21, 22, 23, 24, 25, 26] All authorities agree that the recovery of the organism constitutes the only positive proof of brucella infection but that this is rarely accomplished in the chronic case. Although a high serum agglutinin titer is generally accepted as good presumptive evidence of active infection, the use of the agglutination reaction in chronic brucellosis appears to be of very indefinite value. If negative, as it usually is, it does not exclude brucella infection, and if positive, it is apt to be so in very low dilution. There is lack of agreement as to whether or not agglutination in low dilution is of specific significance. The results of the test may vary in different hands because of variations in technic and antigen. Finally there is disagreement as to what constitutes the transition level between a "low" and a "high" titer. The opsonocytophagic reaction has been attractive to all investigators. From the technical standpoint, however, its reliable performance is difficult. There is no unanimity of opinion as to its significance and its interpretation is often at variance with other and more reliable clinical and laboratory data. Of all the laboratory procedures used in the study of chronic brucellosis, the one most consistently positive

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is the intradermal reaction to brucella antigen. While an occasional false positive reaction may be obtained, most authorities agree that a positive reaction is a reliable indication of a state of brucella allergy. Its use is chiefly limited by the fact that it does not distinguish past from present, or latent from active infection, and also by the fact that an occasional infection fails to result in demonstrable sensitization. A positive skin test does not establish the diagnosis of brucellosis.

If the above discussion constitutes a fair statement of the diagnostic difficulties in chronic brucellosis and, on the other hand, if the assertion is true that the disease is a common cause of chronic illness, it is apparent that there is great need for careful study, from both clinical and laboratory standpoints, of large groups of individuals suspected of brucella infection. In such an investigation the solution of two problems is desirable: a satisfactory method of case finding and the establishment of control groups. Conditions for such an investigation would be ideal if, by the routine application of easily performed, well standardized and well understood tests, the actively infected could be readily identified. There is as yet no method of case finding on these terms but if the investigation be broadened so that brucella allergy instead of active infection be the basis for case selection, then there is a fairly reliable test—the intradermal reaction to brucella antigen. Comparisons of duplicate data from the resultant sensitive and nonsensitive groups will then serve to satisfy the need for control observations.

Table 1 summarizes the source and status of the individuals that we have tested to date. Intradermal tests were performed with Huddleson's Brucellergen on two groups. The first group consisted of 1497 adult patients, all having presented themselves for examination because of some health problem

TABLE I

Source and Status of Subjects Tested

	Number tested	Number positive reactors	Per cent positive reactors
Chronically ill patients			
Private practice: Darley and Gordon	1497	236	15.76
Control or well group			
Physically well patients:			
Colorado Psychopathic Hospital	239	21	8.76
Maternity patients:			
Colorado General Hospital	222	21	9.90
Students:			
University of Colorado	419	46	10.97
Employees:			
Gates Rubber Company	290	32	11.03
Total	1170	120	10.25
Percentage difference between patient and control groups:			5.51

—usually one of long standing. The clinical findings in each case were recorded on form history and physical examination sheets so that the initial work-up was uniform. Adequate laboratory and consultation facilities were available so that the clinical investigation in each instance was complete. Of these 1497 patients, 236 or 15.76 per cent were found brucella sensitive.

The second or control group was made up of 1170 well individuals. One hundred twenty or 10.25 per cent gave positive tests. When this percentage is contrasted with that of the patient group, a difference of 5.51 per cent will be noted. The statistical evaluation of this difference yields a value of 4.24 standard deviations, a figure well above that of the two standard deviations necessary to be of significance. Since more of our controls were under 30 years of age than over and since the reverse was true for the patient group, we have set up table 2 to show the incidence of positive reactors in

TABLE II

Breakdown of Patients and Controls into Subgroups above and below Thirty Years of Age

(The totals are less than those given in table 1 because the ages were not known for all individuals tested)

Twenty-nine and below

	Number tested	Number positive	Per cent positive
Patient group:	296	43	14.52
Control group:	862	85	9.97
Percentage difference:			4.55

Thirty and above

	Number tested	Number positive	Per cent positive
Patient group:	1166	193	16.55
Control group:	268	31	11.56
Percentage difference:			4.99

the two groups for both below and above this age level. The percentage difference between the controls and the patients under 30 years of age was 4.55 and over 30, 4.99. From the statistical standpoint these two figures are just barely at significant levels: the values being 2 and 2.1 standard deviations respectively. It should be stated, however, that these values will become more significant if, in each comparison, the percentage difference does not diminish as the smaller group approximates the larger in size.

It has been pointed out that case selection by intradermal testing will include not only those individuals with active infection but also those whose infections are latent or inactive. At first glance it may appear that the inclusion of positive reactors of the latter two types might dilute any significant data from the first type. The degree to which this may be true depends upon the frequency of the chronic form of the infection. If chronic

brucellosis is at all common, in a study involving a large number of brucella sensitive cases, the emergence of significant trends should not be obscured, particularly since it would be probable that the incidence of active infection would be high in a group of chronically ill, brucella sensitive patients. On the other hand, since brucella sensitization does frequently occur as an incidental finding, any such trends, to be considered significant, must be definite.

Aside from the general statement that chronic brucellosis may constitute a clinical entity in itself, the literature states or implies that the infection may cause or aggravate such syndromes as the allergies,[6] the chronic arthritides [11, 12, 13] and the psychoneuroses.[20, 33, 34, 35] If these statements and implications are sound, it would seem logical to expect the incidence of brucella sensitization to show an increase in association with such conditions. The balance of this report will deal first with findings relative to the possibility of any relationship between brucella sensitization and allergy, chronic arthritis or psychoneurosis and, finally, with evidence that may support the existence of a low-grade, indolent form of chronic brucellosis as a clinical entity.

Dustin and Weyler[6] felt that clinical and laboratory evidence justified a diagnosis of chronic brucellosis in 441 patients. In this group all had a history of allergy in their immediate families. The incidence of personal allergy was 92 per cent. No control observations were noted, no comments as to the types of allergy were included and no attempt was made to interpret the significance of the finding except to correlate it with other observations which they felt justified the conclusion that the symptoms of chronic brucellosis were due to brucella allergy rather than to lowered resistance. One feels the implication, however, that these investigators believe that the individual who has an inherent allergic tendency has thereby an increased susceptibility to brucella sensitization and, a priori, to chronic brucellosis. Although their concept regarding the symptomatology of chronic brucellosis may be plausible, our observations indicate that neither allergy in the immediate family nor personal allergy has any association with sensitization to brucella. By using the most reliable index to family allergy—a family history of hay fever, we found the incidence to be essentially the same in both the sensitive and nonsensitive groups: 13.9 and 13.8 per cent respectively. For the sake of accuracy in our consideration of personal allergy, only diagnoses based upon our own observations were included. Inspection of table 3 makes it apparent that the conditions most commonly regarded as allergic in nature likewise showed no essential differences in frequency between the skin test negative and the skin test positive patients. Migraine is not considered in the study because we feel that it is a symptom complex in which many factors other than allergy may be involved.

The neuroskeletomuscular manifestations in cases of acute and subacute undulant fever are well recognized but any consistent relation between the chronic forms of the infection and the chronic arthritides is questionable. In 1938 Goldfain[11] gave impetus to the consideration when he reported evi-

TABLE III
Allergy Tabulation

	Skin test negative patients			Skin test positive patients		
	Number patients considered	Number cases found	Per cent cases found	Number patients considered	Number cases found	Per cent cases found
Family allergy						
Hay fever	1197	166	13.8	236	33	13.9
Personal allergy						
Hay fever	1261	202	17	236	45	19.1
Asthma	1261	103	8.1	236	15	5.2
Neurodermatitis	1261	82	6.5	236	10	2.3
Urticaria	1261	73	5.8	236	21	8.8

dences of brucella infection in 51 per cent of 157 patients, a preponderance of whom were suffering with arthritic disease. He did not indicate the frequency of the various types of joint conditions but, in another publication [12] dealing with 50 arthritic patients, he reported brucella sensitization in 13 of 19 patients with atrophic arthritis, one with ankylosing spondylitis and seven out of 10 with hypertrophic arthritis. No control observations were included in his reports.

Evidence indicating any significant association of brucella infection and the atrophic type of arthritis has not been uncovered by other investigators. At the 1940 meeting of the American Rheumatism Association we [3] presented evidence against any significant association of brucella sensitization and atrophic arthritis. Green and Freyberg,[16] after careful investigation of 25 patients with atrophic arthritis, were able to demonstrate brucella sensitization in but two instances. Manchester [25] reported 13 per cent of 48 cases of rheumatoid arthritis with positive skin reactions but, after demonstrating sensitization in 11 per cent of 175 nonarthritic patients, he concluded, as did Green and Freyberg, that brucella infection could not be of etiologic significance in this type of joint disease.

Our data underscore the conclusions of Green and Freyberg [16] and of Manchester,[25] for only six, or 7.5 per cent of 80 patients with classical atrophic arthritis gave positive reactions to intradermal brucella antigen. This figure is far below the incidence of positive reactions in our control group of 1170 well individuals. While Goldfain [13] has reported brucella sensitization in five of 18 patients with ankylosing spondylitis, we obtained no reactions in six patients with this condition.

Atypical rheumatoid (subacute infectious, focal infection) arthritis is the one type of arthritis in which the demonstration of brucella sensitization might logically be expected to point the way, at least occasionally, to etiology. Sixty-one of our patients had atypical rheumatoid arthritis and, of these, 11 or 18 per cent were brucella sensitive. This figure, when compared to the 10.25 per cent incidence for the control group, may seem impressive. Three

of the cases were particularly of interest from the brucella standpoint because of their improvement from specific therapy. We feel that a large series of brucella sensitive patients with this type of arthritis should be studied carefully from the cultural and therapeutic standpoints in order that the possible rôle which brucella infection might play in the etiology of the condition might be thoroughly considered.

One of Goldfain's reports [12] hints at a possible relationship between brucella infection and hypertrophic arthritis. Of 1261 skin test negative patients, we found this type of arthritis in 205 or 16.5 per cent, and in 236 skin test positive patients we found the condition in 42 or 17.8 per cent. These two figures are too close to permit any conclusion other than that brucella infection and hypertrophic arthritis have no significant relationship.

Although brucellosis does not appear to be of importance as a cause of chronic arthritis, the literature carries the strong suggestion that subjective rheumatic complaints without objective evidences of joint disease occur with significant frequency in brucella sensitive patients. Angle and Algie [1] reported rheumatic symptoms in 34 per cent of 462 brucella sensitive grade and high school children as against only 6 per cent of 100 skin test negative controls. Calder [4] indicated that joint pain and swelling occurred in almost 50 per cent of 550 patients giving positive reactions to intradermal brucella antiserum, a skin testing material of questionable value. The frequency of cases with objective joint findings was not indicated and no control observations were included. Green and Freyberg [16] obtained positive reactions in nine of 25 patients selected because of rheumatic symptoms and manifestations not characteristic of any of the common types of arthritis. Although all of these nine patients complained of myalgias and arthralgias, none presented physical signs of joint disease. While testing 100 patients with miscellaneous chronic complaints, Manchester [25] found 38 with positive reactions, 55 per cent of which had joint symptoms. He regarded this as significant since only 20 per cent of the 62 skin test negative patients had similar complaints.

Any investigation designed to shed light upon this question must take into account the fact that subjective neuroskeletomuscular complaints without objective evidences of disease are very common in the psychoneuroses. This fact is emphasized by our finding that out of 100 brucella negative patients with personality determined illness, 54 had such complaints (table 4). Consequently, patients with emotional factors in their illnesses were excluded from the groups involved in the following data. As will appear later we have carefully selected 74 skin test positive patients in whom we felt a diagnosis of chronic brucellosis was justified. Muscle and joint discomforts were present in 65 per cent of this group. For control purposes we selected a group of 110 skin test negative patients with no objective evidence of any type of joint disease. Subjective rheumatic symptoms were present in 38 per cent of this group—a figure sufficiently below the 65 per

TABLE IV

Symptom Tabulation

(Figures expressed as per cent)

Symptoms	74 cases of probable brucellosis	62 cases of psychoneurosis, brucella positive	100 cases of psychoneurosis, brucella negative
Fatigue, weakness	80	77	81
Neuroskeletomuscular discomfort	65	63	54
Back ache (including neck)	32	45	40
Low	24	32	32
Interscapular	8	5	
Neck ache	7	8	8
Joint pain	26	26	21
Generalized aching	22*	13	14
Neuropsychiatric	57	79	76
Emotional instability	7	30*	30*
Irritability	26	34	32
Tension, anxiety	19	53*	55*
Depression	23	30	17
Insomnia	23	40	26
Headache	43	58	66
Migrainous	11	13	15
Non-migrainous	36	50*	51*
Digestive	40	59	81
Constipation	19	35*	33*
Indigestion	30	51*	59*
Diarrhea	5	3	6
Fever	34*	8	11
Nasal congestion	31	27	38
Dizziness	24	23	40
Sweating (spontaneous)	23*	14	24
Heart consciousness	20	47*	30
Chilliness	13	3	18
Urinary	13	14	25
Paresthesias	12	24*	27*
Abdominal pains	12	30*	38*
Chest pain (not anginal)	11	13	18
Menstrual (female patients)	28	45*	46*
Pain	19	30	25
Excessive flow	9	22	10
Scanty flow	5	5	7
Irregularity	2	10	4
Miscellaneous data (values not expressed as per cent)			
Number females	43	40	67
Number males	31	22	33
Average age (years)	35	44	37
Average number of symptoms	6	8*	8*
Average duration of symptoms (years)	3.5	8*	5.8*

* Figures considered of significance.

cent noted for the brucella sensitive group to be impressive as far as the association of brucella sensitization and subjective neuroskeletomuscular complaints is concerned.

In an article published in 1934, Alice Evans,[7] in writing of chronic brucellosis, made a series of significant statements: ". . . the textbook definition of neurasthenia describes chronic brucellosis: exhaustion, insomnia,

irritability and complaints of aches and pains for which no objective signs can be found. . . . There is no doubt that chronic brucellosis is often diagnosed as neurasthenia. . . . These facts challenge the right of a physician to make a diagnosis of neurasthenia . . . without considering . . . the possibility of chronic brucellosis."

Since 1934 most authors dealing with the subject of brucellosis have referred to and have agreed with the essence of these statements. A few have gone further and have considered brucella infection as a major cause of neurasthenia.[20, 33, 34, 35] Although such a wholesale viewpoint disregards the accepted concepts of psychopathology, the superficial clinical resemblance of chronic brucellosis to neurasthenia, and to the other psychoneurotic reaction types, justifies analysis and discussion. In table 4 will be found a comparison of the symptomatology of our group of 74 patients with probable brucellosis with that of 100 skin test negative psychoneurotic patients which emphasizes the clinical similarity of the two groups. In addition to this symptom similarity, it should be pointed out that paucity of objective physical findings and static chronicity were equally common to both.

It is possible that a chronic infection such as brucellosis could help lessen resistance and contribute to conditions which might favor the development of neurotic symptoms or of a neurotic attitude. Neurotic symptoms do not necessarily in themselves reflect a clinical psychoneurosis, but a situation responsible for neurotic symptoms, particularly if a neurotic attitude has developed, can readily lead to a personality determined illness. Finally, since brucella sensitization is so common and since chronic brucellosis itself may also occur frequently, the occurrence of both sensitization and active infection in the psychoneurotic is inevitable. In other words, given a brucella sensitive patient with neurasthenic symptoms, one may be confronted with a real problem in differential diagnosis. The patient may have chronic brucellosis or psychoneurosis or both. The presence of one does not rule out the possibility of the other. However, if brucella infection is commonly involved either as a primary or as an aggravating cause of personality determined illness, it would be reasonable to expect brucella sensitization to be decidedly increased in a large group of such patients. If this line of reasoning is correct, our findings oppose the premise that brucellosis is a very significant factor in the etiology or aggravation of the psychoneuroses. We considered that emotional and personality factors were playing a significant rôle in the illness of 702, or 46.9 per cent of the 1497 patients skin tested to brucella. Of these 702 patients, 114 or 16.2 per cent were brucella sensitive. When compared with the 15.7 per cent positive incidence for the total group of 1497, this figure is robbed of any significance. This conclusion is further borne out by a comparison of the number of psychoneurotic patients in the brucella negative with the brucella positive group: 588 or 46.6 per cent for the former and 114 or 48.2 per cent for the latter. The difference between the two percentages is too small to warrant consideration.

If two fundamentally different conditions present a similar clinical picture, psychologic and therapeutic considerations make correct discrimination a matter of paramount importance. We consider this to be the case in the evaluation of brucella infection and personality malfunction. Every possible means for the differentiation of the two conditions must be resorted to. As has been pointed out in the introduction of this paper, much is to be desired from the brucellosis side of the problem because there are no reliable laboratory methods available for the selection of the actively infected case. From the psychiatric standpoint, the mental status examination [32] will, in the majority of instances, help with the evaluation of the patient from the personality standpoint. Careful judgment is essential. In general it is our conclusion that given a brucella sensitive patient, a personality determined illness must be considered before a diagnosis of chronic brucellosis should be seriously entertained. In other words, a diagnosis of chronic brucellosis should be challenged until the possibility of psychoneurosis has been evaluated.

The final object of this paper is to establish evidence for or against the existence of a low-grade indolent form of brucellosis as a clinical entity in which, except for the usual presence of skin sensitivity, confirmatory laboratory findings are frequently indeterminate or absent. In other words, can the demonstration of brucella sensitization to any degree serve as a foundation for the selection of patients in whom a clinical diagnosis of chronic brucellosis is to be seriously considered?

In order to isolate the cases of brucella sensitization most likely to have active infection, it was felt necessary to consider only those cases in which every other possible significant diagnosis had been excluded. Diagnosis by exclusion is not a sound clinical principle, but as far as this investigation is concerned, we felt that it was the only approach for the selection of the actively infected from a fairly large group of brucella sensitive patients. It is probable that many patients were discarded in whom active infection may have been an illness factor. Thus, of 236 patients found to be skin test positive, all but 49 were omitted from consideration as possible cases of chronic brucellosis because of other disease or findings that could have accounted for their complaints. To this 49 it was possible to add another 25 patients selected just as carefully from cases referred for consultation because of positive reactions to intradermal brucella antigen. Thus a total of 74 cases of probable chronic brucellosis was available for clinical study. The data have been organized with the view of identifying any symptomatology that might characterize an indolent type of the infection. The symptomatic tabulation of the 74 patients is given in the first column of table 4. The most common symptoms are listed in the order of their frequencies. Since it was apparent that the symptom pattern was very similar to that often found in the psychoneurotic patient, a similar tabulation for 100 skin negative psychoneurotic patients was added for comparison. Comparison of the brucella positive with the psychoneurotic group reveals the same symptom

order and, with few exceptions, no striking differences in symptom frequency. Generalized aching, low-grade fever and spontaneous sweating were more frequent in the brucella group, whereas psychic and nervous symptoms, nonmigrainous headache, digestive symptoms, heart consciousness, abdominal pains, paresthesias, menstrual disturbances and a greater number and duration of complaints were more common to the psychoneurotic patients. As far as individual symptoms were concerned, it was not felt that anything peculiar or constant that would differentiate either group was apparent.

Physical examination of all patients included in the tabulation, brucella positive as well as psychoneurotic, revealed no findings of significance.

A comparison of our data with the literature dealing on the one hand with proved brucellosis and on the other with other clinical studies of brucella sensitization, should be of interest. Table 5 represents an effort to

TABLE V

Comparative Symptom Tabulation
(Figures expressed in per cent)

	Proved brucellosis	Studies of brucella sensitization					
	Hardy* 300 cases	Calder* 550 cases	Manchester* 38 cases	Manchester* 62 controls	Darley and Gordon 74 cases	Angle and Algie 562 cases	Angle and Algie 100 controls
Fatigue, weakness	100	89	45†	50†	80		
Neuroskeletomuscular			53	17	65	34	6
Back ache	47	63			32		
Neck ache	28	57			7		
Joint pain	33	49			26		
Generalized aching	43	66			22		
Neuropsychiatric	50	87			57	44	26
Insomnia	35	54			23		
Headache	63	69	25	4	43	37	15
Constipation	55	57	20	25	19	15	2
Indigestion			37	30	30		
Fever	100	85	25	2	34	5	1
Dizziness		18			24		
Sweating	83	49	17	1	23		
Chilling	78	51			13		
Abdominal pain	33	48			12		
Menstrual (female patients)		60			28		
Pain		42			19		
Excessive flow		30			9		

* Figures transposed from a graph.
† Figure also includes "nervousness."

brief such a comparison. The study of Hardy et al.[18] represents a very complete clinical analysis of acute and subacute brucellosis. At the opposite extreme of infection level is the contribution of Angle and Algie[1] who reported the mass symptomatology for 462 brucella sensitive school children. These investigators found a much higher incidence of chronic complaints in this group than was found in 100 skin test negative controls. No effort was made to cull out the asymptomatic children, of which there must have been

quite a number. Consequently their figures may be lower than they would otherwise have been. We consider this work to be of considerable significance, not only because it was controlled but because positive allergic tests in children are in general of more clinical importance than they are in the average adult. Differences in the methods of classifying and tabulating symptoms complicate the comparison but from the table it is apparent that the symptom frequencies for our group of chronic cases are intermediate between those for the acute cases of Hardy et al. and the sensitized cases of Angle and Algie. Furthermore, except for the fever, chills and sweats incident to the acute infectious state, the type of symptoms and the order in which they occurred were essentially constant throughout.

Four other reports, each in many respects similar to ours, deserve comment. For the sake of completeness we have attempted to add the symptom summaries from two of these to our table. While at first glance Calder's [4] data appear to be in general agreement with ours, we do not feel justified in stressing the fact because the reliability of antiserum as a skin testing material has yet to be established,[9, 10] because in all probability the figures are elevated due to the inclusion of many cases of acute brucellosis, because data were included from every patient giving a positive skin test regardless of the presence of other disease and finally because no control observations were reported. Manchester's [25] 38 cases of probable brucellosis are difficult to compare with ours because of a different type of symptom tabulation. Tiredness, easy fatigability and nervousness were listed together as a single category. The author did not indicate that psychoneurotic patients were excluded from his study and it may be that the higher incidence of these symptoms in his control group was due to the inclusion of such patients. A third paper by Griggs [15] and a fourth by Urschel [37] together cover an aggregate of 153 patients who presented essentially the same order and frequency of symptoms as noted for our group of patients.

After first excluding every other possible explanation for symptoms, the skin testing of patients presenting a picture similar to that which we have reported in our 74 cases should constitute a good test of the case which we have tried to establish for "indolent brucellosis." The literature yields two reports of such an approach to the problem and in each instance we consider that a significant score was obtained. As has been mentioned, Manchester found 38 positive reactors in 100 patients all of whom before testing presented a picture compatible with a diagnosis of chronic brucellosis and similarly Urschel [37] found 70 positive reactors among 124 such patients (56.4 per cent).

Before the consideration of any laboratory observations, we again wish to emphasize that our grouping of brucella sensitive patients was based entirely upon clinical grounds. It was not until after the groups had been established that the results of agglutination tests were tabulated and credited to each group. The rapid technic with concentrated antigen was the method used, only agglutinations performed before intradermal testing were re-

corded and all positive reactions, weak or strong, were tabulated. Table 6 contains the summary of the results. Attention is first called to the finding that positive agglutinations were obtained in only 7.26 per cent of all the skin test negative patients as compared with 38.3 per cent for all of those skin test positive. To us, however, the most significant finding was that of positive agglutination reactions in 50.8 per cent of the patients whom, from the clinical standpoint, we felt were the most likely candidates for active chronic brucellosis. The results of the opsonocytophagic tests were not tabulated according to groups because of 177 tests, 164 or 92.5 per cent gave readings

TABLE VI

Tabulation of Agglutination Reactions

	Number of tests	Number positive according to agglutination titer					Total number positive	Per cent positive
		1–25	1–50	1–100	1–200	1–400		
Skin test negative patients	1010	20	31	21	1		73	7.26
Skin test positive patients	217	12	27	24	12	8	83	38.3
Cases of probable brucellosis	61	3	10	10	3	5	31	50.8
Cases of psychoneurosis	40	1	2	3	1		7	17.3
Cases discarded	116	8	15	11	8	3	45	38.8

low enough to indicate very little or no immunity. Blood cultures, the few times taken, were negative.

We feel that a review of our data seems to favor the entity of "indolent brucellosis" but in doing so it emphasizes that while certain clinical and laboratory characteristics may appear rather definite for a group of such cases, they are not marked enough to be of practical help when it comes to the consideration of the individual patient. Consequently it is again emphasized: given a brucella sensitive patient, a diagnosis of chronic brucellosis can not be seriously regarded as probable until every other possible explanation for symptoms has been carefully considered.

CONCLUSIONS AND SUMMARY

Of all the laboratory methods available for the study of chronic brucellosis, the one most consistently positive is the intradermal test. The indiscriminate use of this test, however, is limited by the fact that it does not distinguish past from present or latent from active infection. In spite of these limitations, our finding that brucella sensitization occurred significantly more often in the chronically ill than in the well, would seem to indicate that brucella infection was frequently involved in chronic ill health and also that sensitization must to a considerable degree parallel active infection.

Using these premises as a working basis, it was our purpose to make a careful clinical analysis and study of a large group of patients skin tested with brucella antigen in order to determine first, if brucella infection could be involved as an etiologic or aggravating factor in such conditions as the

allergies, the chronic arthritides or psychoneuroses and second, if a low-grade, indolent form of brucellosis could be identified as a clinical entity.

As to the first consideration, our data were opposed to any idea that brucella infection might be of etiologic or contributory importance in allergy, chronic arthritis or psychoneurosis. In the discussion of joint disease, however, a plea was made for further investigation of the possibility in atypical rheumatoid arthritis.

The second consideration was based upon the concept that careful clinical study of the brucella sensitive patient can with reasonable accuracy establish the presence or absence of active infection. It was emphasized that every possible explanation for symptoms must be carefully considered before a diagnosis of chronic brucellosis is justified. In this regard, because of the superficial resemblance between psychoneurosis and what we consider chronic brucellosis, we feel that the former possibility should always be ruled out. We were able to present data from 74 patients in whom we felt a diagnosis of chronic brucellosis was probable. The most frequent symptoms encountered were: fatigue, muscle and joint aches and pains, non-migrainous headache, digestive complaints and low-grade fever. Significant physical abnormalities were conspicuous by their absence. The incidence of positive agglutination reactions was significantly high in the group. We feel that a discussion of our findings in the light of the available literature appears to favor a low-grade type of chronic brucellosis as a clinical entity.

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HEPATIC CIRRHOSIS AS A COMPLICATION OF CHRONIC ULCERATIVE COLITIS *

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That form of colitis which is generally called "chronic ulcerative colitis" is one in which a great many complications arise. This is not surprising in view of its chronicity, the marked structural changes which develop in the colon, the opportunity these afford for the spread of infection through the bowel wall, and the nutritional deficiencies which are so common during the prolonged course of the disease.

Most of the complications of chronic ulcerative colitis involve the colon itself, or the perirectal tissues, and include such well recognized conditions as polyposis, stricture of the colon, carcinoma of the colon, and perirectal abscesses. In addition to these, a number of systemic complications of chronic ulcerative colitis have been described. Bargen, in listing 558 complications occurring in 1500 patients with chronic ulcerative colitis, makes mention of such complications as arthritis, cutaneous lesions, renal insufficiency, endocarditis, phlebitis, splenomegaly, ocular diseases (of which iritis is the most important), peripheral neuritis, progressive arterial occlusion, and multiple abscesses of the liver. The occurrence of nutritional deficiency as a complication of chronic ulcerative colitis has also been stressed (Mackie). This may be recognized by the presence of characteristic changes in the skin, tongue, and mucous membranes, by the development of edema, or by the demonstration by roentgen-ray of changes in the pattern of the small intestine.

It is rather surprising to note the rarity with which hepatic complications have been observed during the course of ulcerative colitis. Pylephlebitic abscesses of the liver are evidently strikingly infrequent, having been reported by Bargen in only two of the 1500 patients reviewed by him. Others who have studied large groups of patients with ulcerative colitis have also encountered relatively few in whom hepatic disease could be demonstrated. Thus, such reviews of the disease as those of Bargen, Jackman and Kerr, Feder, Hurst, Jankelson and his associates, and Streicher make practically no mention of liver disturbances associated with colitis. Although splenomegaly is mentioned as being found in some patients (in 14 of the 1500 of

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The peritoneoscopic examinations mentioned in the case reports were performed by Dr. Wilbur W. Oaks.

Bargen's series) this has been usually considered to be a response to infection rather than the result of hepatic disease.

Comfort, Bargen and Morlock have reported four instances in which chronic ulcerative colitis was associated with hepatic insufficiency. All four of the patients had long-standing and relatively mild bowel disease with minimal anatomic changes in the colon. In three of these the colitis antedated the liver disease and in these three the colitis was thought to have been responsible for the development of the hepatic disturbance. These authors believed that injury to the liver by infection was of primary importance as a cause of the hepatic insufficiency.

Cain and Callen have been the only authors to emphasize the possibility that changes in the liver may be significant in the course of severe colitis and expressed the opinion that fatty hepatic degeneration appears often in the terminal stages of suppurative recto-colitis. Ratnoff and Patek, in their review of cirrhosis have quoted statistics from Oriental sources to the effect that in India, China and the Philippines the incidence of dysentery in patients with cirrhosis ranges from 25 to 40 per cent as compared with control series in which the incidence of dysentery was from 7 to 17 per cent.

Since hepatic disturbances of major significance have been observed so infrequently as complications of ulcerative colitis, we are reporting the following group of five patients.

Case Reports

Case 1. M. C. S. Female. Age 14.

This patient was first admitted to the Graduate Hospital in April 1939. Diarrhea had begun one year prior to this. A diagnosis of amebic dysentery had been made, although the basis for this diagnosis is unknown. Seven months before this admission, pain had developed in the right upper abdomen. Because this was thought to be due to possible amebic abscess, laparotomy was performed. Empyema of the gallbladder was discovered and the liver was found to be small and cirrhotic.

Following this operation, the patient had remained well until August 1939 when diarrhea recurred. Examination at that time revealed marked emaciation, some peripheral edema, and abdominal distention. The liver was palpable across the epigastrium, and the spleen was found to be enlarged. Sigmoidoscopic examination revealed the mucosal changes of chronic ulcerative colitis.

The significant laboratory findings included reduction of the total proteins to 5.05 and of the albumin to 2.02, reduction of the total cholesterol to 83, of which the esters were 23 milligrams per cent, bromsulfalein retention of 4 per cent and a suspiciously positive galactose tolerance test (2.43 grams of galactose being excreted after the ingestion of 40 grams of the sugar).

Roentgen-ray studies of the small bowel revealed changes considered characteristic of avitaminosis and hypoproteinemia. Barium enema was not entirely successful, but the portion of the left colon visualized showed considerable mucosal pathology with polypoid hyperplasia in the region of the splenic flexure. The changes were considered diagnostic of chronic ulcerative colitis. The patient was discharged from the hospital on a program designed to correct the nutritional disturbances, but she continued to have severe diarrhea. Anorexia became pronounced and further weight loss resulted. Mild jaundice appeared. The patient was re-admitted for a few days in May 1940, quite toxic and febrile. Slight icterus was present. The tongue was

smooth and red. The abdomen was distended and definite ascites could be demonstrated. The spleen and liver were enlarged. The latter organ was firm and somewhat nodular.

Very few laboratory studies were performed. These revealed moderate anemia, extreme hypoproteinemia (albumin 1.99 grams per cent), a serum bilirubin of 3 milligrams per cent and bromsulfalein retention of 4 per cent.

Because the patient was considered to be moribund, her parents were permitted to remove her from the hospital. She died shortly after this. No autopsy was obtained.

Comment. This 14 year old patient had been found to have hepatic cirrhosis a few months after the onset of the symptoms of chronic ulcerative colitis. During the subsequent course of her illness, she developed splenomegaly, jaundice, enlargement of the liver, and evidence of liver dysfunction. The cirrhosis may have been responsible for the hypoproteinemia and the ascites, and may have also contributed to the difficulty of maintaining satisfactory nutrition.

Case 2. J. M. Male. Age 45.

Fourteen years prior to hospital admission, in September 1943, this patient had had a rectal operation of unknown character. For many years he had consumed large quantities of alcohol, and it is possible that his diet had not been adequate although information regarding this was indefinite. The general health had remained satisfactory until one year previously when a single rectal hemorrhage had occurred. There were no other symptoms until one month before admission when severe bloody diarrhea began. This was associated with fever, sweats and weight loss, but not with abdominal pain or tenesmus.

When admitted to the hospital the patient was quite toxic, and his temperature was 104 degrees. He was moderately emaciated and the tongue was red and angry in appearance. The heart was enlarged and a diffuse systolic murmur was heard. The abdomen was distended, but no ascites could be demonstrated. The spleen was palpable and the liver was definitely enlarged, being easily felt across the epigastrium. There was marked perirectal infection and numerous sinus tracts around the anus discharged pus. Sigmoidoscopic examination revealed a sanguino-purulent exudate in the rectum and sigmoid. The mucous membrane visualized was coarsely granular with numerous bleeding areas, and showed definite hyperplastic and polypoid changes. The initial diagnosis was acute fulminating recurrence of chronic ulcerative colitis, complicated by severe perirectal infection, sepsis and both hepatomegaly and splenomegaly. The presence of multiple liver abscesses was considered possible.

The significant laboratory findings (table 1) at this time included the demonstration of moderate anemia and of mild hyperglycemia, and also of slight hypoalbuminemia. Barium enema revealed diffuse ulcerative colitis with extensive polypoid changes.

Initial therapy consisted of a high protein, high caloric diet, with insulin for a short time, ample vitamin supplements, sulfasuxidine and liberal transfusions of blood and plasma. The immediate result was unsatisfactory. Evidence of a profound toxic state persisted and severe diarrhea continued. A peri-anal abscess formed, but evacuated itself. Gradually, however, there was a decrease in the severity of the symptoms, and some improvement in the patient's status. It was observed, however, that the liver had become larger and that its border was somewhat irregular. Peripheral edema appeared and the presence of ascites was demonstrated. Marked palmar erythema was also noted. Evidence of hepatic dysfunction was found in slight hyperbilirubinemia, bromsulfalein retention and lowered levels of both the total

TABLE I

Laboratory Findings in Patient J. M. (Case 2)

Date	9/7	9/20	10/1	10/28	11/4	11/23	12/6	12/13	1/13	1/25	2/3	2/15	2/26	3/14	3/30	4/10
R.B.C. (Millions)	3.6	3.8	4.5	4.0	3.7	3.8	3.9	3.2	3.9	4.1	4.1	3.7	4.3	3.9	3.7	4.5
Total Protein	6.7	6.5	7.6	6.2	6.2	5.6	8	8	5.6	6.5	4.5	5.8	5.7	5.1	6	5.8
Serum Albumin	3.5	2.9	3.4	3.7	2.8	2.9	2.7	3.6	2.4	2.8	1.8	2.7	2.2	2.3	2.6	2.8
Serum Bilirubin			0.2	1.0	0.6	0.4		0.4	0.2	0.2		0.2	0.2			0.2
Total Cholesterol	188				134		146	150						106		109
Cholesterol Esters	73				64		100	95						60		71
Bromsulfalein Retention					6	15			17	8			15	10		
Cephalin Flocculation		2+				4+										4+
Prothrombin % Normal					75		45		61			61				

and esterified blood cholesterol. The serum albumin remained well below normal, despite high protein feedings and the liberal use of plasma and amino acids intravenously.

Although numerous diuretics were administered, the ascites increased so that it was necessary to tap the abdomen. The fluid obtained was clear and had the physical properties of a transudate. When the ascites re-accumulated, peritoneoscopy was performed. This showed no evidence of intra-abdominal malignancy. The omental veins were very distended. The picture presented by the liver was that of a pronounced cirrhosis with diffuse nodularity of the surface of the organ.

During the latter period of hospitalization, there was slight improvement in the patient's general condition. The diarrhea became less severe and the gross blood disappeared from the stools. The ascites decreased somewhat with the continued use of diuretics. As can be seen, however, from the following table, which lists the pertinent laboratory findings, liver dysfunction persisted and also the hypoalbuminemia, despite the administration of considerable amounts of blood and plasma.

The patient left the hospital on May 16, 1941 to continue on a high protein diet and vitamins. A few weeks later, however, he died rather suddenly. The details of the immediate cause of death are unknown.

Comment. This patient with severe fulminating colitis involving much of his colon also had definite cirrhosis. This resulted in enlargement of both the liver and spleen, ascites, and laboratory evidence of hepatic dysfunction. There was also persistent hypoalbuminemia. The diagnosis of cirrhosis was established by peritoneoscopy. The past history of this patient included alcoholism, associated with dietary deficiencies. The colitis may, therefore, not have been the only factor in the production of the cirrhosis.

Case 3. M. S. Male. Age 51.

When this patient was first seen in December 1943 he stated that he had had diarrhea for approximately 20 years. A diagnosis of chronic ulcerative colitis and rectal stricture had been made. The stricture was dilated but the diarrhea persisted, and over a long period the patient had up to 10 bloody movements daily. Finally, about two years before the original visit, the stricture was treated surgically, the patient was given sulfasuxidine and some improvement followed.

When the patient was first studied, the only significant abnormality was the demonstration by sigmoidoscopic examination of changes in the rectum and sigmoid,

quite typical of ulcerative colitis. Diet and sulfasuxidine were prescribed and, since there was symptomatic improvement, the patient discontinued visits. He returned in July 1945, stating that he had recently experienced intermittent mild diarrhea, but that weakness was pronounced and that a weight loss of 20 pounds had occurred. Sigmoidoscopic examination again showed evidence of moderately active colitis. A striking physical finding, however, was the presence of a large, firm and somewhat irregular liver. The spleen was not enlarged. There was neither edema nor ascites.

The laboratory studies revealed moderate anemia. The serum bilirubin was normal. A cephalin cholesterol flocculation test was positive. The hippuric acid synthesis was moderately reduced and there was 15 per cent bromsulfalein retention. Prothrombin time was normal.

Peritoneoscopy was performed. A small amount of ascites was found. The liver was uniformly enlarged, its surface was granular with small punctate hemorrhagic areas. A few larger nodules were seen. A biopsy taken from the right lobe of the liver demonstrated the presence of definite periportal cirrhosis.

Since the establishing of the diagnosis of cirrhosis, the patient had been treated with a high protein, high vitamin, smooth diet and vitamin supplements, liver injections and transfusions. It has been difficult to maintain a satisfactory blood count, although the diarrhea has been relatively mild and little blood is lost by bowel. Repeated laboratory studies indicate varying degrees of liver dysfunction as shown by fluctuating bromsulfalein retention and changes in the reaction of such tests as the cephalin cholesterol flocculation test and the thymol turbidity test. The liver has remained large and firm. No ascites has been recognized on physical examination.

Comment. This patient had had colitis for many years before liver disturbance was recognized. The first clinical evidence of the latter was the hepatomegaly and the presence of liver disease was then established by both laboratory studies and peritoneoscopy. Because the colitis had been present for so long before the development of cirrhosis, it is possible that the bowel disease contributed to the evolution of the cirrhosis.

Case 4. A. B. Female. Age 60.

This patient was originally admitted to the Graduate Hospital in October 1944. She had developed diarrhea three years before this during a period of intense nervous tension. It had recurred at relatively long intervals but during attacks the diarrhea was moderately severe, blood being passed with many of the movements. Despite the diarrhea the general health had remained satisfactory. There had been no weight loss.

General physical examination was negative, but the sigmoidoscopic findings were characteristic of active ulcerative colitis with moderate hyperplastic changes. Laboratory examinations showed mild anemia and hyperglycemia. The serum bilirubin and serum albumin and prothrombin time were normal. No detailed liver function tests were done at this time. Barium enema revealed the roentgen picture of ulcerative colitis involving the bowel distal to the hepatic flexure.

With treatment consisting of diet, rest, and sulfasuxidine, and investigations of some of the factors responsible for the nervous tension, there was prompt subsidence of symptoms, and the patient was discharged to the care of the family physician.

Following this period of hospitalization there were further recurrences of the diarrhea during periods of worry. Because of the marked severity of one of these recurrences, and the passage of numerous bloody stools, the patient was re-admitted to the hospital in January 1946. Physical examination was again essentially negative. The liver and spleen were not enlarged. Sigmoidoscopic examination, however, again showed active colitis.

A moderate anemia was present, but the blood sugar, serum bilirubin, and urine urobilinogen were normal. The serum albumin, however, was definitely decreased (to 2.49 grams per cent on one occasion), and the presence of hepatic dysfunction was indicated by bromsulfalein retention and positive response to the cephalin cholesterol, thymol turbidity and serum colloidal gold tests. The hippuric acid synthesis, however, was found to be normal. The barium enema again revealed colitis distal to the mid transverse colon with changes suggesting polypoid hyperplasia.

Peritoneoscopic examination showed no ascites. The liver was normal in size, its surface pale and studded with numerous uniform small nodules. The gross appearance of the organ was that of cirrhosis. Punch biopsy of the liver confirmed the diagnosis of cirrhosis.

On treatment such as had been given before, symptoms again subsided and the patient is now being treated with a smooth, high protein diet with vitamin supplements.

Comment. The diagnosis of cirrhosis in this patient was based upon the liver function tests, the peritoneoscopic examination, and the biopsy since there was no clinical evidence of hepatic disease. Because the cirrhosis was demonstrated in this patient after the colitis had been present for about five years, it is possible that the colitis may have contributed to the development of the liver disease.

Case 5. L. G. Female. Age 23.

Approximately six years prior to hospital admission in 1945, when the patient was 17 years old, she had experienced a change in bowel habit and had begun to have mushy stools. From time to time after this, short periods of bloody diarrhea occurred, particularly in association with nervous tension. The diarrhea had apparently never interfered with normal activities, and the patient had been considered well enough to enter the WAC, two years before admission to the Graduate Hospital.

Shortly after she entered the Army, a pustular rash appeared on the abdomen and extremities. No satisfactory diagnosis of the nature of this rash was reached, and it remained resistant to treatment. Three months after the appearance of the rash an illness characterized by fever and jaundice resulted in admission to an Army hospital. Roentgenogram of the colon, taken at this time, revealed changes later recognized as those produced by chronic ulcerative colitis. Because bowel symptoms were slight when these films were taken no significance was attached to these findings then. Despite various forms of therapy, low grade fever, slight jaundice, malaise, mild diarrhea and the rash recurred for prolonged periods during the two years that the patient remained in the Army. Because of the persistence of the illness she was referred to the Graduate Hospital in May, 1945.

At the time of admission, the temperature was 99° F., but this fluctuated considerably during the period of hospitalization, occasionally reaching 104° and usually being 100°. Pallor and inconstant jaundice were present. A few scattered papular and pustular lesions were noted over the lower abdomen and the extremities. The liver was enlarged, firm and smooth, but not tender. The spleen was also enlarged. The sigmoidoscopic picture was that of a moderately active chronic ulcerative colitis.

Moderate anemia was present and the serum albumin was consistently lowered to levels of between 3 to 3.5 grams per cent. The serum bilirubin fluctuated considerably, from 0.5 to 3.8 milligrams per cent. The total cholesterol was 164, the esters being 109. At admission the prothrombin time was decreased to 45 per cent of normal, but later rose to 75 per cent. A galactose test was border line positive (2.35 grams of sugar being excreted in the urine). The alkaline phosphatase level was elevated to 22 Bodansky units. There was definite bromsulfalein retention rang-

ing from 15 to 30 per cent. The cephalin cholesterol, thymol turbidity and serum colloidal gold tests were all strongly positive. Blood cultures and various agglutination tests were negative. Biopsy of the skin lesions and of a lymph node failed to reveal significant findings. By barium enema changes typical of chronic ulcerative colitis were demonstrated throughout the entire colon. There was no evidence of small bowel disease.

Peritoneoscopic examination showed both liver and spleen to be markedly enlarged. The liver was mottled and granular in appearance and presented the gross picture of cirrhosis. A satisfactory biopsy was not obtained.

Treatment consisted of rest and a high protein, low fat diet with vitamin supplements, transfusions and sulfasuxidine. There was some symptomatic response, but the febrile reaction persisted throughout the seven weeks that the patient remained in the hospital. From time to time diarrhea became more severe and sigmoidoscopic examinations then revealed evidence of increased activity of the colitis. The patient was discharged in June 1945 without definite improvement.

Comment. This patient presented evidence of marked hepatic dysfunction and a peritoneoscopic picture of cirrhosis six years after the apparent onset of her colitis. Although the colitis itself had not produced a great deal of disability, it was evidently more severe than was suggested by the diarrhea, because of the continued fever and the general ill health. The skin rash may have been a complication of the colitis. The colitis may have also been a factor in the evolution of the cirrhosis.

Discussion

These five patients in whom definite and advanced liver disease was found were encountered during a period in which 151 patients with chronic ulcerative colitis were studied. In our experience, therefore, the association of parenchymal hepatic disease with ulcerative colitis has not been unusual, although the paucity of reports on the association of these two conditions suggests that it occurs but rarely.

In four of these five patients, clinical evidence suggestive of the liver disturbance was noted during the period of treatment for the colitis. The possible presence of hepatic disease was indicated by such findings as enlargement of the liver, or of both the liver and the spleen, ascites and jaundice. In only one patient were there no clinical features such as these. In this case, recognition of the hepatic disorder depended upon the performance of liver function tests and subsequent peritoneoscopy.

The incidence of liver disease in cases with chronic ulcerative colitis may be even greater than our present report suggests. It is possible that the routine use of liver function tests would demonstrate that hepatic dysfunction exists in not a few patients with ulcerative colitis. At the present time, one of us (J. F. M.) is conducting a survey of patients with colitis to determine the frequency with which they suffer liver dysfunction of a sub-clinical degree. This survey includes an analysis of the value of the various liver function tests in the recognition of hepatic disorders in patients with colitis. We shall omit from this paper, therefore, a discussion of the relative merits of the different tests which were used in the study of these patients.

We believe, however, that mention should be made of the hypoalbuminemia which was found so consistently in the four of our five patients in whom the serum albumin level was determined. In the three of these who presented clinical evidence of liver disease, all of the determinations of serum albumin levels during the periods of hospitalization were well below the normal accepted by our laboratories (4 to 4.5 grams per cent). In the patient who had no clinical manifestation of hepatic involvement, the serum albumin was normal at the time of the original visit but dropped to 2.9 grams per cent at a subsequent admission.

Numerous disease conditions may, of course, lead to the development of hypoalbuminemia. This is not unusual in uncomplicated ulcerative colitis because of the frequency of inadequate food intake and the loss of protein substances in the bloody and purulent bowel discharges. We have been impressed in the past, however, by the prominence of hypoalbuminemia as a biochemical change in advanced liver disease and by the difficulty of restoring the serum albumin to a normal level when this had become lowered in the cirrhotic patient (Tumen and Bockus). Failure of response to measures which usually elevate the serum albumin level which has been depressed by nutritional deficiency or protein loss was a striking feature in the patients reported here. The hypoalbuminemia persisted despite a large protein intake and liberal administration of plasma and amino-acids by vein. This strongly suggests the importance of hepatic dysfunction in contributing to the hypoalbuminemia of these patients, and leads us to conclude that liver disease should be searched for in patients with ulcerative colitis who have decreased serum albumin that does not respond to the usual therapeutic measures. In a sense, persistent lowering of the serum albumin may be regarded as a "liver function test," and its demonstration should bring to the physician's attention the possibility of the co-existence of severe liver disease.

In four of the five patients reported here, full recognition of the presence of cirrhosis was made possible by peritoneoscopy. This method of examination proved entirely safe, even in patients whose general health had been seriously impaired by the presence of severe colitis. Our experience with these and other patients gives additional support to the confidence expressed by Benedict in the value of peritoneoscopy in the diagnosis of liver disease. When various laboratory procedures suggest that hepatic dysfunction, and possibly cirrhosis, may be present, peritoneoscopy is an invaluable procedure which can confirm or disprove this diagnosis quite rapidly and safely.

The finding of two such apparently unrelated diseases as ulcerative colitis and cirrhosis in the same patient calls for some study of possible connection between them. It must first be admitted that the two diseases may be unrelated to each other and that their association may be merely a coincidental one. Cirrhosis has been found in from 1 to 6 per cent of cadavers studied at routine autopsy (Tumen). In the case of our patient, J. M., alcoholism and dietary deficiencies may well have contributed to the development of

cirrhosis, even if he had never contracted his severe colitis. The discovery of cirrhosis in these five patients with ulcerative colitis, however, indicates to us that other factors than mere coincidence must be considered in attempting to explain the finding.

A few investigators have believed that severe colitis may be a manifestation of underlying liver disease. This opinion was expressed by Dimitresco Popovici and by Saccone and Repetto. These authors have stated that hepatic insufficiency is to be considered as the underlying disturbance producing the tissue changes which favor the development of colitis. They believe that the bowel disorder should be regarded as a local complication of the general systemic changes which have been produced by hepatic disease. The evidence presented in support of this opinion, however, has seemed to us to be rather inconclusive. The infrequency with which hepatic insufficiency has been observed in the past in patients with colitis is likewise against the viewpoint that a liver disturbance should be considered the primary cause of ulcerative colitis, as is also the fact that colitic disease has rarely been noted in the autopsy examination of patients dying of cirrhosis.

A study of our patients has convinced us, on the other hand, that severe and prolonged colitis may readily produce changes in the patient which lead to the development of cirrhosis. We, therefore, believe that cirrhosis may occur occasionally as a true complication of colitis. Some support is to be found for our opinion in the age and sex distribution of our patients, even though our group is admittedly so small that no statistical conclusion can be considered to be justified. Two of our patients were quite young, being only 14 and 23 years old. Cirrhosis at this age level is quite rare. Of the entire group of 151 patients with colitis, 68 were male and 83 were female. Of the five with cirrhosis, two were male and three were female. This sex distribution of the cirrhotic patients is perhaps not striking, but it does reverse the usual sex incidence of cirrhosis. The finding in this small group of patients with cirrhosis of two young individuals and of three women is at least suggestive of the possibility that the presence in these patients of ulcerative colitis may have contributed to the development of the cirrhosis.

The etiology of cirrhosis is still somewhat obscure. At present it is best to regard it as the end result of a variety of injuries to the liver—nutritional, toxic, infectious, and circulatory—rather than as a disease that is produced by the effect of a single agent. Recently, of course, great emphasis has been placed, and correctly so, on nutritional deficiencies as the cause for cirrhosis. Whether in the human, nutritional disorders alone can produce cirrhosis is not yet entirely clear.

In a patient with colitis, numerous factors conspire to furnish a background in which the development of cirrhosis need not be surprising. There is first, of course, the element of malnutrition, the importance of which in the colitis patient must be stressed again and again. Many patients with colitis receive inadequate diets. This is a result of anorexia, fear of certain

needed foods, and the lack of emphasis by the attending physician upon the need for a diet that is adequate in protein and all vitamins as well as in total caloric value. Bowel hypermotility and nutritional changes in the small intestine lead to faulty absorption of what food is taken. As a consequence of these factors, many patients with active ulcerative colitis admitted to a hospital can be shown to have signs of deficiency diseases which involve numerous organs, and which produce anemia and hypoproteinemia. An added cause of malnutrition and hypoproteinemia in the colitis patient, one that is usually unrecognized, is the loss of large amounts of protein substances in the discharges of blood, mucus and pus from the bowel. There are, unfortunately, few studies of this loss, but it is obvious that the amount of protein that leaves the body in this way can be very large. In determinations of protein loss by bowel of two patients, carried out by Monaghan, it was found that the daily rectal discharges contained from 25 to 30 grams of protein. Since one of these patients had had an ileostomy, and one was receiving nothing by mouth during the period of observation, it may be concluded that the amount of protein found in the rectal discharges came exclusively from the colon. The effect of continuous loss of this kind on the general body economy can be appreciated readily.

Ulcerative colitis usually runs a prolonged and chronic course. A victim of this disease can therefore suffer for long periods with deficiencies which injure the liver, finally to the point at which that organ is unable to play its part in the metabolism of proteins and vitamins. Secondary hepatic breakdown may then serve to perpetuate the nutritional disturbances which have contributed to its origin.

The general toxic state which often persists for so long in the colitis patient may also add to the injury of the liver. This is difficult to evaluate. The prolonged fever and general ill health contribute to the anorexia. They also increase the metabolic requirements and thus aggravate the nutritional defect. The toxic state may also induce mild degenerative changes in the liver which make it more susceptible to further damage by continued deficiencies. It is also necessary to mention the possible effect on the liver of the constant absorption of toxic material and bacteria from the bowel. This also is difficult to measure in any accurate way. The absorption of these materials, however, can be conceived as placing an added burden on the detoxifying functions of the liver as well as possibly directly injuring the liver cells. Further knowledge concerning the effect of the local bowel disease on the liver status must await more detailed studies of hepatic function in large groups of patients with colitis.

Finally it is necessary to inquire regarding the possible effect of the presence of the complicating liver injury on the course of colitis. Our five patients represented varying degrees of severity of colitis. In two of our patients the colitis was quite severe and the patients died within from 16 to 22 months after the appearance of colitic symptoms. In two of the patients the colitis was prolonged and resistant to treatment and the patient's general

health had been chronically impaired. In only one of the patients was the colitis of the intermittent and relatively mild type that responds fairly easily to rest, sedation, and similar general measures. This was the patient in whom there was no clinical evidence of liver disease, the presence of this being first suspected after the performance of liver function tests. In this patient, also, hypoproteinemia was not observed at the initial examination but was noted subsequently. There would seem to be, therefore, some rough parallel between the severity and ease of recognition of the liver disturbance and the severity of the colitis, although an investigation of a much larger group of patients is necessary before definite conclusions regarding this can be reached. It would not be unexpected, however, to find that the patients in whom severe liver damage exists are those with the more severe degrees of colitis. The presence of protracted bowel disease naturally leads to greater nutritional disturbance so that more marked liver injury is produced. This in turn increases the tendency to hypoalbuminemia and makes it more difficult to maintain the patients in protein and vitamin balance and preserve the satisfactory nutritional status so necessary for recovery from a disease such as ulcerative colitis.

Conclusion

1. Among 151 patients with ulcerative colitis, five were encountered with cirrhosis. Two of these patients were much younger than those in whom cirrhosis is usually found, and three of the five were women.

2. In four of these five patients there was clinical evidence of the liver disease. In one there were no signs or symptoms of cirrhosis, but the presence of this was suspected because of abnormal responses to hepatic function tests. It is possible that routine use of liver function tests in patients with ulcerative colitis would reveal an even higher incidence of hepatic damage in this disease.

3. In four of the five patients the diagnosis of cirrhosis was established by peritoneoscopy, a procedure which proved safe and well tolerated in these individuals.

4. In four of the five patients the cirrhosis probably developed as a complication of the colitis. In the fifth patient it was difficult to conclude that this was the case because of an antecedent history of alcoholism and dietary deficiency.

5. A striking biochemical feature of the studies of these patients was the demonstration of hypoalbuminemia that persisted despite the strenuous application of therapeutic measures which ordinarily restore a lowered serum albumin level to normal. This suggests that hepatic disease is important in producing the hypoalbuminemia of these patients.

6. It seems probable that the development of cirrhosis in patients with colitis results chiefly from nutritional deficiencies, although the effect of general toxemia and of the absorption of toxic substances from the bowel

may be important in this respect. The nutritional deficiencies probably arise chiefly from defective diet and faulty absorption of proteins and vitamins. The loss of large amounts of proteins in the rectal discharges may, however, contribute significantly to the development of a deficiency state.

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CARDIOLOGIC CRITERIA FOR THE DIAGNOSIS OF RHEUMATIC HEART DISEASE IN THE APPARENTLY HEALTHY SUBJECT *

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THE cardiac manifestations of rheumatic fever have a special diagnostic importance for several reasons. First, they determine the importance of the disease to the health and life of the patient. Second, they are the sole manifestations which may persist in the patient after recovery from the acute phase. Finally, they are the only signs of rheumatic disease in the apparently healthy subject on the basis of which a foregoing episode of acute rheumatic fever may be recognized or suspected.

The application of cardiac signs to the diagnosis of rheumatic heart disease is complicated, however, by the difficulty in interpreting observed phenomena, and by the inconstant significance of some of the physical signs. Because of the obvious importance of diagnosing rheumatic heart disease when it exists, and of avoiding a mistaken diagnosis of this disease when it does not exist, it is the object of this paper to discuss the significance of the cardiac observations which may be the basis for a diagnosis of rheumatic heart disease.

The cardiac signs which may be found in the clinically inactive phase of rheumatic disease are residua of the signs which were present in the acute episode. Even when cardiac signs appear for the first time during apparent quiescence, in patients whose acute rheumatic episode produced no evidence of cardiac damage, they follow the same patterns as when the signs of cardiac involvement originated in an acute episode. Accordingly the interpretation and significance of these signs is in many respects the same in the acutely ill patient into whose differential diagnosis rheumatic fever enters as in the apparently healthy subject in whom a chance finding of an abnormal cardiac sign raises the suspicion of rheumatic heart disease.

The problem of evaluating cardiac findings will here be discussed primarily in terms of their implication as to the presence of heart disease in the apparently healthy subject. This evaluation is becoming increasingly important with the greater recognition of rheumatic fever as a problem in public health, for such findings occur not infrequently in the examination of new patients, in surveys of schools and communities or as chance discoveries in patients.

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A. *Diastolic murmurs.* These murmurs cause little difficulty in diagnosis since the two groups of murmurs heard in this phase of the cardiac cycle happen to be those which are almost invariably associated with organic valvular changes, mitral stenosis or aortic insufficiency.

1. The apical diastolic murmur as found in the apparently healthy subject is almost a certain indication of rheumatic heart disease and mitral stenosis. In the child it usually does not take the form of the classical crescendo presystolic rumble ending in the snap of the first mitral sound. More frequently it appears as a softer sound, mid-diastolic in time, rumbling in quality, which ceases before the first sound at the apex. However, in some children, especially those who have sustained considerable cardiac damage, it may appear in the classical "adult" form described above. This murmur may or may not be accompanied by an apical systolic murmur of mitral insufficiency, depending on the orifice of the stenosed valve.

A distinction should be made here between the active and inactive rheumatic patient. In the former a mid-diastolic murmur, blowing rather than rumbling in quality, may be heard at the height of an acute episode involving mitral insufficiency, and may regress and disappear leaving at most an apical systolic murmur as the patient improves. Under these circumstances a diagnosis of mitral stenosis cannot, of course, be made.

2. The aortic diastolic murmur is again pathognomonic of an organic valvular lesion, aortic insufficiency, and in the age groups in which luetic aortitis is quite unlikely it strongly suggests rheumatic heart disease. This murmur is again likely to appear in form somewhat different in children from that in adults. In children it may be heard only at the left border of the sternum in the third interspace, rather than at the classical aortic area. It also has a very hollow, sighing quality, as compared with the more low-pitched and full-bodied aortic diastolic murmur of adults. The direction of transmission of this parasternal diastolic murmur, when it is sufficiently intense, is in a diagonal line toward the apex. However, even when the examiner hears this transmitted murmur first at the apex its difference in quality from the somewhat rumbling apical diastolic of mitral stenosis should indicate its origin.

B. *Systolic murmurs.* These are more variable and difficult of interpretation.

1. The pulmonic systolic murmur. A systolic murmur, of a considerable range of intensity and pitch, may be heard in many normal hearts of children and young adults. In children it has been heard in as many as 60 per cent of normal subjects,[1] and among all age groups the data of the Medical Impairment Study of several life insurance groups showed only a 12 per cent increase of mortality among such subjects above the general expectation.[2] Since a pulmonic systolic murmur is a frequent normal finding, and since rheumatic pulmonic stenosis is very rare, no significance can be attributed to the pulmonic systolic murmur as a cardiac finding under the circumstances. It should be noted only for a baseline physical description of the subject.

Similarly in the acutely ill patient the finding of a pulmonic systolic murmur does not favor the diagnosis of rheumatic fever or, in the presence of definite signs of rheumatic fever, of rheumatic heart disease.

2. The aortic systolic murmur. Occasionally a systolic murmur may be heard at the second interspace to the right of the sternum. This may be accepted in children and young adults as evidence of aortic valve involvement by a rheumatic process. There are two exceptions to this conclusion, however. First it must be ascertained that this murmur is not merely transmitted from the pulmonic area. Second, in young adults, a very soft and labile systolic aortic murmur may be caused by the emotional tachycardia and hypertension of physical examination. This possibility can be tested by repeated examinations.

If no other explanation can be found for the presence of a systolic murmur in the aortic area and it is taken to indicate rheumatic involvement of that valve, such a finding does not constitute the basis for a diagnosis of aortic stenosis. The latter is rare, even in rheumatic hearts which have suffered a series of damaging episodes. The criteria for diagnosing aortic stenosis include a harsh aortic systolic murmur transmitted, with a thrill, into the vessels of the neck, low pulse pressure and left ventricular hypertrophy.[3]

3. The precordial twang. In many children a murmur is heard over the precordium, frequently including the area of the apex, which is also of no significance. This was perhaps best described by Still [4] as similar to the sound produced by the twanging of a tense string. A very low-pitched string of a bass-viol might also produce such a twang. The murmur is so low-pitched that it lacks a blowing quality. In fact its pitch is quite similar to that of the first apical sound itself, so that the effect is one of a prolongation of the first sound almost until the second sound, offering difficulty to the examiner in deciding precisely when the first sound really ends. This is in contrast to the case of the murmur of mitral insufficiency, in which the examiner hears the thud of the first sound give way to the more blowing effect of the murmur. This precordial twang is rarely recognized as such in general practice, probably because of the poor contrast in quality between the first apical sound and the succeeding murmur, and because little attention is directed to it in the literature. It is often either overlooked entirely by the referring physician where rheumatic heart disease is not otherwise suspected or is called an apical systolic murmur where there is suspicion of rheumatic disease. In the latter case, or when it is observed in routine examination, it has not infrequently been the basis for a mistaken diagnosis of rheumatic heart disease with mitral insufficiency. The likelihood of this misinterpretation is enhanced by the fact that this sound may be of moderate intensity, and that the point of maximum intensity, although usually in the midprecordium or somewhat below it, may be quite near the apex. As in the case of the pulmonic systolic murmur the presence of this

murmur does not favor the diagnosis of rheumatic heart disease in the well or ill subject.

4. Systolic murmurs at the apex. Systolic murmurs heard at the apex of the heart present the most difficult problems in the cardiologic diagnosis of rheumatic heart disease. A consideration of these murmurs emphasizes the importance of complete description of a cardiac murmur in terms which include quality, intensity, extent of transmission, point of maximum intensity and constancy. Some of these attributes make it possible to classify some of the murmurs heard at the apex in terms of their significance.

First, a systolic murmur heard at the apex may be the result of transmission of a pulmonic systolic murmur across the precordium. As the examiner explores the precordium for the point of maximum intensity of the murmur under these circumstances, the discovery that the sound is loudest at the base indicates that it has no more significance than the pulmonic systolic murmur.

Second, murmurs are not infrequently heard at the mitral area whose point of maximum intensity is to the right of the apex, either halfway to the sternal border or at that line. Although very little has been published of such murmurs it seems quite improbable that they have their origin in insufficiency of the mitral valve. Therefore these are also in all probability without significance for the diagnosis of rheumatic disease.

Third, there are murmurs heard at the apex which disappear or show marked variation in intensity in the course of the respiratory cycle, the cardio-respiratory murmurs. These are, of course, also without pathologic significance.

Finally there are soft murmurs heard at the apex in some cases of high fever, tachycardia and anemia. If correction of these features results in disappearance of the murmur they also are thereby shown not to imply disease.

On the other hand if a moderate or loud systolic murmur heard at the apex in the course of a routine examination is of maximal intensity at that point, of blowing quality, and transmitted toward the axilla it is probably well to assume that there is mitral insufficiency due to rheumatic heart disease.

The greatest difficulty arises in the case of the incidental finding of a systolic murmur maximal at the apex, of low or moderate intensity and blowing quality, transmitted very little or not at all to the left. In such cases no diagnosis can be hazarded until the following steps are taken.

1. Fluoroscopy in antero-posterior and oblique positions or teleroentgenography, to determine enlargement of the heart. If there is evidence of enlargement the murmur should be taken as evidence of organic disease of the heart. However, many subjects with mitral insufficiency do not show cardiac enlargement.

2. Electrocardiography. The electrocardiogram is of little value in inactive rheumatic heart disease, since only a small number of rheumatic

patients show changes in this stage. These may occasionally be residua of the changes which occurred in the active phase, or evidence of auricular hypertrophy or ventricular preponderance attributable to rheumatic lesions, but they cannot be said to be characteristic of rheumatic disease.

3. History. If a satisfactory history of a rheumatic episode in the past is elicited, the apical systolic murmur may be assumed to represent a residual mitral insufficiency. Such a history should include an authentic account of carditis, migratory polyarthritis or chorea by a physician, or a history of acute joint or muscle pains accompanied by obvious signs of infectious disease.

4. The laboratory findings associated with active rheumatic disease would not be of help here, since they are merely indicators of the presence of acute infection. However, in a subject in whom the cardiologic findings warranted a diagnosis of rheumatic heart disease an elevated erythrocyte sedimentation rate or leukocytosis might indicate some degree of activity of the rheumatic process at the time.

Unfortunately even if all of the above have negative results it is still not possible to say that the murmur may not be a residue of active rheumatic heart disease, and thus point to this diagnosis. A definite percentage of subjects with chronic rheumatic heart disease are unaware of a previous attack of rheumatic infection. Such patients, according to Scott [5] have been "variously estimated at 20 to 25 per cent" of all rheumatic subjects. This estimate is consistent with the data of Fineberg and Steuer [6] who followed for 6 to 15 years 100 children in whom only an apical systolic murmur was found. Thirteen per cent of the 45 children who had no history of rheumatic disease went on to further cardiac lesions, whereas the comparable rate among the children with such a history was 50 per cent, or four times as great. Even when a history is available, it is too often unsatisfactory, involving the patient's or his parents' description of joint or muscle pains, choreiform movements, rash, et cetera. Typical migratory polyarthritis, the one sign of rheumatic disease which is sufficiently dramatic to give rise to a satisfactory description by the layman, occurs in only a minority of all cases of rheumatic disease, comprising about a quarter of one series of 700 cases (Wilson [7]).

C. Enlargement of the heart. This physical sign, although it provides strong evidence per se of organic disease of the heart, will be only briefly mentioned here, because a rheumatic heart whose enlargement is sufficient in degree to be detected on physical examination will almost invariably have accompanying murmurs. In the usual sequence of events the examination by roentgen-ray for cardiac enlargement is carried out in an effort to provide evidence as to the organic nature of a murmur discovered on physical examination. In such cases evidence of enlargement of the left auricle or of either ventricle by the roentgenographic technics mentioned above makes almost certain the organic significance of the murmur.

A difficult problem arises in the management of subjects with unsolved apical systolic murmurs, that is, subjects without evidence of cardiac enlargement, electrocardiography, history of rheumatic infection, or transmission of the murmur. This group certainly includes some with damaged hearts, for life insurance statistics show a mortality of 56 per cent above the expected rate.[2] On the other hand certainly not all of these subjects have rheumatic heart disease, since the group who have a history of rheumatic fever or chorea to explain their apical systolic murmur show a mortality which is very much higher.

The diagnosis of a rheumatic heart disease cannot, then, be made solely on the basis of a systolic murmur confined to the apex. Nor does the correct management of the patient demand an immediate diagnosis, since the treatment is essentially the same in both cases. All such patients should be seen periodically at intervals varying up to six months, according to the circumstances of the case, with physical examinations at each visit and laboratory, roentgen-ray and electrocardiographic examination at longer intervals.

In the meantime the presence of the murmur as an adventitious sound which has not yet been fully explained should be made clear to the patient or to his parents, and the patient may be allowed normal physical activity except for competitive sports.

It is not possible to say how long such observation must be continued before the patient can be told that the murmur is without significance. If after a few semi-annual examinations there is no progression of the murmur or other evidence of rheumatic disease it is very unlikely indeed that rheumatic heart disease is present. Nevertheless there have been instances of recrudescence of rheumatic heart disease after many years. Even among patients who recovered from acute rheumatic fever with no trace of cardiac damage Bland and Jones [8] found as many instances of onset of cardiac signs in the second five-year period following the acute infection as in the first five years. There were a few cases in which cardiac signs appeared even in the second decade. Other studies have shown similar cases of long delayed reactivation.

The impossibility of making a definite decision as to the presence of rheumatic heart disease for a considerable length of time emphasizes the importance of following such subjects without creating the impression that they are "heart patients."

This discussion has emphasized rather more than might be expected the avoidance of a mistaken diagnosis of rheumatic heart disease, in comparison with the opposite error. There are two reasons for this. First, with the increasing attention which is being directed at rheumatic heart disease there will be increasing numbers of mass examinations, and school and community surveys, with the object of discovering unknown cases of rheumatic disease. The failure to classify properly the innocuous adven-

titious sounds and the failure to withhold a diagnosis where it cannot properly be made may create considerable confusion and in addition may ultimately do as much harm for many non-rheumatics as it will do good for the rheumatic patients discovered. Of a group of 11 children referred for study to the Rheumatic Clinic of the Philadelphia General Hospital as a result of one school survey, only three were found to have murmurs which were thought to have a possible pathologic significance. Second, the psychological effect on patient and family of a diagnosis of heart disease is so profound and far-reaching, and its effect on initiating cardiac neuroses so great, that it is essential to avoid such an effect when it is not necessary.

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THE ACTION OF CARBON DIOXIDE IN WATER MOBILIZATION *

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"Although changes in the properties and activities of cytoplasm probably explain many of the changes in distribution of body water, at present data are not available which permit a description in these terms. The least we can do is to cease speaking of the distribution of various ions as if they were always excluded from certain phases of body water," Darrow.[1] The previous statement is in complete agreement with that of Peters and his associates [2] who, as the result of their studies on "Osmotic Adjustments Between Cells and Serum in the Circulating Blood of Man," state: "Analysis of the experimental data presents only a paradox, . . . base traverses the cell membranes in a highly capricious manner which cannot serve the interest of osmotic equilibrium. . . . It is suggested that base may be transferred in behalf of cellular metabolism rather than osmotic pressure."

Since carbon dioxide is one of the most common products of tissue activity we have focused our interest on this product. From our observations we have been forced to conclude that the accumulation of carbon dioxide within the tissues results in increased hydration, while the decrease of carbon dioxide is accompanied by decreased hydration.

The Effect of Decreasing Carbon Dioxide

Hyperventilation. During hyperventilation there occur: (1) a fall in carbon dioxide tension of the alveolar air, (2) a decrease in the carbon dioxide combining power of the venous plasma, (3) a marked decrease in urine acidity with an increased elimination of phosphates, and (4) diuresis, for example, hyperpnea for 20 minutes may increase the urinary output from 56 c.c. per hour to 123 c.c. per hour and hyperpnea for 32 minutes may increase the urinary output approximately fivefold (from 46 c.c. to 220 c.c. per hour).[3, 4, 5]

It is evident that hyperventilation (carbon dioxide elimination) yields more free water with better secretion and better excretion.

Reduction of the Carbon Dioxide Combining Power of the Plasma (Alkali Reserve). Agents, including hyperventilation, which produce a decrease in the carbon dioxide combining power of the plasma promote diuresis; ammonium chloride is such an agent. We have observed that the administration of 18 grams of ammonium chloride (12 capsules of 7.5 grains daily for three days) produced weight loss in 80 per cent of the 39 subjects studied, the average weight loss being 1.97 pounds per individual.[5]

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The Effect of Increasing Carbon Dioxide

Red Blood Cells absorb water from the plasma when carbon dioxide is passed through blood; this was demonstrated by Limbeck [6] as early as 1894 and it has been repeatedly confirmed. The red blood cells of the venous blood absorb carbon dioxide and water from their environment and as a result increase in size. The reaction may be expressed as follows:

$$CO_2 + H_2O \xrightleftharpoons[\text{carbonic anhydrase}]{} H_2CO_3$$

$$\boxed{KHbO_2} + \underbrace{H_2CO_3 + H_2O}_{\text{Venous environment}} = O_2 + \boxed{\begin{matrix} HHb \\ KHCO_3 \\ H_2O \end{matrix}}$$

Arterial red blood cell — Venous red blood cell

Increasing the Carbon Dioxide Combining Power of the Plasma (Alkali Reserve). Increasing the carbon dioxide combining power of the plasma is accompanied by an increase in body water. We have noted [5] that the administration of 36 grams of sodium bicarbonate (4 grams t.i.d. for three days) produced a weight increase in 90 per cent of the 49 subjects studied; the average weight gain being 2.28 pounds per individual.

Increase in Muscle Weight During Exercise. Ranke (1865) [7] probably was the first to demonstrate that the stimulation of muscle was accompanied by an increased uptake of water. During the activity of skeletal muscle the muscle increases in weight and this is accompanied by a marked change in the distribution of water and electrolytes.[8, 9, 10] Carbon dioxide production is associated with the activity of skeletal muscle; therefore it is reasonable to consider that the accumulation of carbon dioxide might be a factor in the increased hydration of muscle during its activity.

Experimental

The hydrophilic capacity of frog muscle was determined without, and with the presence of carbon dioxide, using: distilled water and graduated concentrations of the following: sodium chloride, ammonium chloride, hydrochloric acid, sodium hydroxide, glucose, urea, sodium bicarbonate, monobasic, and dibasic sodium phosphate.

Frog legs were sectioned at the hip joint, skinned, and the entire limb and foot were weighed, and placed in 100 c.c. of the test fluid contained in 150 c.c. beakers. The muscles were weighed again at the end of 4 hours and 20 hours. In some experiments the muscles were weighed each hour.

Table 1 is presented to show the hydration which occurred during 4 hours and 20 hours when the frog legs were immersed in distilled water. It will be observed that the fluid containing the muscles was subsequently

subjected to carbon dioxide for four hours; this was accomplished by placing the beakers on plate glass and covering them with a bell jar. The carbon dioxide was introduced through a side vent in the bell jar. The administration of carbon dioxide was accompanied by a decrease in the weight of

TABLE I

Solution Used	4 Hrs.	20 Hrs.	CO_2 4 Hrs.
Triple Distilled H_2O	+ 54	+ 69	− 13.8
Triple Distilled H_2O	+ 58	+ 77	− 14.3
Triple Distilled H_2O	+ 58	+ 84	− 14.
Triple Distilled H_2O	+ 61	+ 72	− 12.
Triple Distilled H_2O	+ 67	+ 83	− 16.
Triple Distilled H_2O	+ 50	+ 71	− 12.

the hydrated muscles. The numbers recorded represent the per cent of gain or loss in terms of the original weight of the muscle.

An agent which causes dehydration of tissue has to exert its action in one of two ways: either by decreasing the hydrophilic capacity of the tissue or increasing the concentration of the solution surrounding the tissue. In order to test this conception, frog legs were immersed in distilled water and immediately placed in an atmosphere of carbon dioxide; chart 1 illustrates the results of this procedure. The muscles reached their maximum hydration in four hours and subsequently began losing water. It will be noted

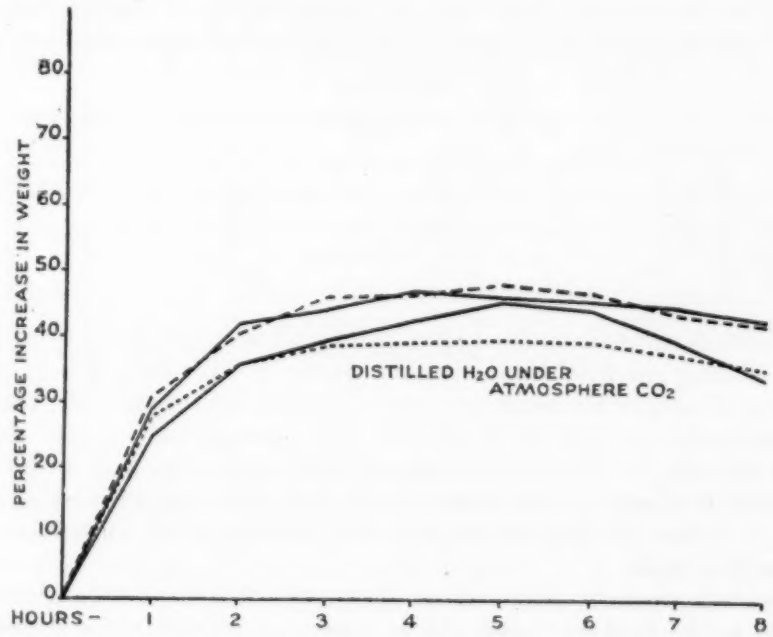

CHART 1.

that the hydration in the presence of carbon dioxide is much less than that occurring in untreated distilled water.

Since carbon dioxide exerted a dehydrating effect on hydrated muscle and also inhibited the hydration of muscle immersed in distilled water, we considered the possibility that this action might be due to the acid action of carbonic acid. Therefore, we next determined the effect of hydrochloric acid, and table 2 is a record of the results obtained with various concentra-

TABLE II

Solution Used	4 Hrs.	20 Hrs.	CO_2 4 Hrs.
HCl N/10	+ 32	+ 49	+ 2.8
HCl N/20	+ 39	+ 65	+ 1.3
HCl N/40	+ 42	+ 59	− 4.2
HCl N/80	+ 60	+ 69	− 8.5
HCl N/160	+ 53	+ 59	− 16.

tions of hydrochloric acid. In only one respect are the results comparable with those obtained with carbon dioxide; the higher concentrations of hydrochloric acid, N/10–N/40, markedly retarded hydration during the first four hours. However, during the next 16 hours there was an increased hydration in such concentrations. At the end of 20 hours the solutions containing the muscles were subjected to an atmosphere of carbon dioxide with the result that the muscles in the more acid solutions continued to increase in weight, while those in the more dilute acid lost weight.

The results obtained with various concentrations of sodium hydroxide are presented in table 3; analysis of the data presents some interesting con-

TABLE III

Solution Used	4 Hrs.	20 Hrs.	CO_2 4 Hrs.
NaOH N/10	+ 63	+ 81	− 8
NaOH N/20	+ 61	+ 82	− 13
NaOH N/40	+ 70	+ 81	− 15
NaOH N/80	+ 61	+ 77	− 11
NaOH N/160	+ 67	+ 78	− 9

trasts with those obtained from corresponding concentrations of hydrochloric acid. During the first four hours the degree of hydration was essentially the same in each of the concentrations of sodium hydroxide used; compared with hydrochloric acid the hydration was approximately double that obtained with the N/10 acid. At the end of 20 hours the total hydration in alkali was markedly greater than in acid, and when subjected to an atmosphere of carbon dioxide the muscles lost weight in all concentrations of sodium hydroxide.

The data we have presented reveal the fact that the addition of carbon dioxide to the fluid surrounding a hydrated muscle will cause dehydration of the muscle; also, if carbon dioxide is present throughout the experiment

the muscles swell less than in distilled water. The question arises: is this effect of carbon dioxide due to a decrease in the hydrophilic capacity of the muscle or is it due to the increase in ion concentration of the fluid surrounding the muscle? The fact that isosmotic solutions of urea are not isotonic prompted us to test the effect of urea. Chart 2 illustrates urea solutions

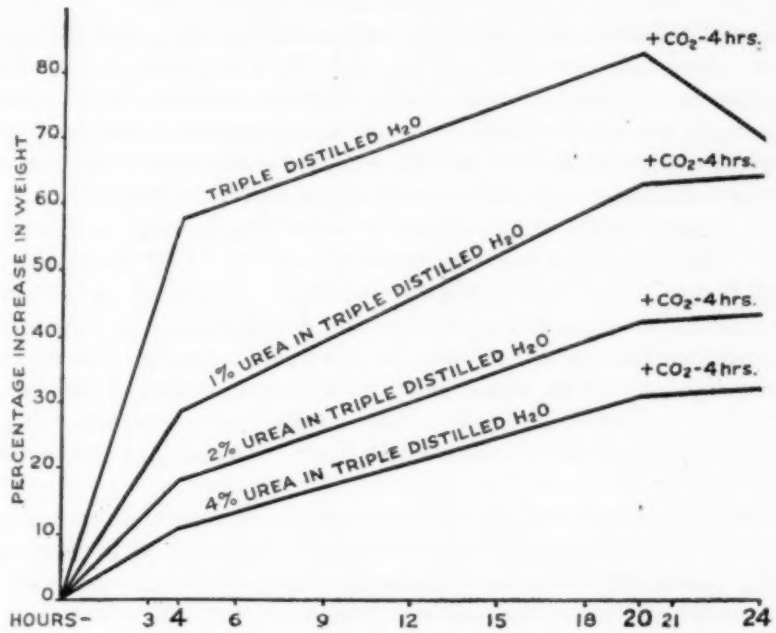

CHART 2.

without and with the presence of carbon dioxide. Since a 2 per cent urea solution is approximately isosmotic with mammalian physiological salt solution it is evident that urea does not establish an isotonic condition. It will be observed that the carbon dioxide atmosphere for four hours did not cause a fluid loss but instead a slight gain in weight was recorded, the gain being practically identical in all concentrations of urea.

DEDUCTIONS

We have presented direct and indirect evidence to support the claim that absorption of water occurs in regions where carbon dioxide accumulates (venous blood) and secretion occurs in regions supplied by arterial blood, which is relatively low in carbon dioxide content. The kidney illustrates both secretion and absorption; the secretion occurring in the region supplied by arterial blood, and the absorption in the region of the venous supply. Normally carbon dioxide accumulates in the tissue and blood of the absorb-

ing area of the kidney and reacts with the tubular contents. The reaction may be expressed as follows:

$$(CO_2 + H_2O \xrightarrow[\text{carbonic anhydrase}]{} H_2CO_3)$$

$$\underset{\text{Tubular urine}}{Na_2HPO_4 + H_2O} + \underset{\text{Tissue}}{H_2CO_3} = \underset{\text{Tissue-Blood}}{NaHCO_3 + H_2O} + \underset{\text{Urine}}{NaH_2PO_4}$$

In a previous discussion of this mechanism we have stated, "Normally the disodium phosphate does not pass through the kidney due to the fact that the sodium salt of such a weak acid dissociates and the free sodium ions combine with the carbon dioxide of the blood stream. During hyperventilation the carbon dioxide of the blood is depleted and allows the sodium to pass as the disodium phosphate, exerting a diuretic action." [5]

This interpretation of the reaction within the kidney is supported by Pitts.[11] The analysis of his experimental data on "The Renal Regulation of Acid Base Balance" prompted him to state: "Carbonic acid dissociates within the cell to form hydrogen ions and bicarbonate ions; the hydrogen ions are exchanged for sodium ions in the tubular lumen; and the sodium ions, accompanied by an equivalent number of bicarbonate ions are reabsorbed into the tubular blood." His studies were concerned with the mechanism for acidifying the urine and he did not consider water mobilization.

We are of the opinion that the accumulation of carbon dioxide in tissues produces an increased acidity which leads to the addition of base and the resulting combination becomes more hydrated. The direction in which the base and water move depends upon the degree of acid in the tissue cells, and the degree of alkali reserve of the blood in contact with the tissue. Increasing the alkali reserve affords more available base which diffuses from the higher to the lower concentration, increasing the hydration of the tissues. With decreased alkali reserve the base and water of the tissue cells tend to move toward the blood stream, decreasing the hydration of the tissues.

Some Responses Which Illustrate the Application of the Above Interpretation

Gaseous Exchange and Fluid Balance. Armstrong [12] has shown that men subjected for four to seven hours daily to a simulated altitude of 12,000 feet in low-pressure chamber develop polyuria in which the urine output was increased 100 to 300 per cent above normal. More recently he states,[13] "the cause of the increase was not apparent."

The fluid balance of unanesthetized white rats in a low-pressure chamber responds to altitudes in a manner corresponding to human beings. The urine output at 10,000 feet altitude is not significantly different from the normal control figure, but at 15,000 feet altitude equivalent the urine in-

crease amounts to approximately 150 per cent and at 25,000 feet 300 per cent.[14]

Swann et al.[15] have also observed a negative water balance in rats during exposure to low barometric pressure. They concluded that anoxia was the main causative factor producing the negative water balance and based such a conclusion on the fact that the administration of oxygen prevented the phenomenon. They also observed that a mixture of 10.5 per cent oxygen and 89.5 nitrogen, maintained at the normal pressure of 760 mm. Hg, did not prevent the phenomenon.

The present author is of the opinion that the negative water balance, resulting from low barometric pressure, is due to the low oxygen content which stimulates respiration and thereby depletes the carbon dioxide of the body; the sequence of events is that previously outlined under hyperventilation diuresis. The respiratory response to increased altitude is stated by Armstrong,[13] as follows: "This varies in different individuals but it has been noted as low as 4,000 feet. At first, only the depth of breathing is increased which is an effective means of increasing the oxygen in the lungs since in shallow breathing very little fresh air gets past the dead air spaces. At about 12,000 feet altitude the increased depth in breathing amounts to between 20 and 100 per cent increase in lung ventilation."

Blood Volume Response to Temperature Changes. Animals exposed to low temperatures respond by shivering and increased muscle tone; this results in hemoconcentration and an increase in intracellular water. If the central nervous system becomes sufficiently chilled to cause general neuromuscular depression the movement of fluid is then in the opposite direction, and the result is subcutaneous edema and hydration of the blood.[16, 17] It is evident that temperature changes, with accompanying changes in metabolic activity, can alter the hematocrit and blood cell count.

Posture and Fluid Mobilization. Numerous investigators have demonstrated changes in plasma volume resulting from postural changes and exercise.[18, 19, 20, 21, 22] A diurnal fluctuation of 10 to 15 per cent in serum protein, dependent upon postural factors, has been shown to occur regularly in individuals during normal existence.[23] This fluctuation is doubtlessly related to the alkaline tide and probably finds its explanation in the observations of Leathes.[3] He focused his attention on the part played by respiration in the production of the morning alkaline tide. While his chief interest was in the reaction of the urine accompanying the hyperventilation on awakening, his data also show a marked increase in urine production. It should be kept in mind that an individual at bed rest with complete muscle relaxation may normally have a plasma volume above the accepted normal, and a serum protein concentration below the accepted normal.

Conclusion

Gaseous exchange plays a part in the mobilization of body fluid.

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PRESCRIPTION OF PHYSICAL MEDICINE BY THE INTERNIST *

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Adequate and successful use of physical agents can be expected only when they are prescribed in a thoughtful and scientific manner. It is the duty, therefore, of physicians prescribing physical medicine to use similar accuracy and detail as when prescribing drugs. In both instances instructions are given to an intermediary highly skilled in technical matters, but untrained in diagnosis. Full advantage of the physical therapist's technical skill can be obtained only by indicating the nature of the condition to be treated and the specific effects to be expected from therapy. The choice of agents to be used should be determined by the physician and an intelligent selection can be achieved solely through knowledge of the actions of the various physical therapeutic measures. As a background for prescription writing it is therefore in order to consider briefly some of the known effects of physical agents on various tissues of the body. As physical agents act primarily from the exterior, it is logical to consider first their effect on the superficial structures.

Skin

Most forms of physical therapy have some effect upon the skin, and we will accordingly discuss some of the primary changes which can be evoked.

Temperature Increase. In considering methods of increasing the temperature of the skin it is well to review the elementary physics involved. The most familiar means of heating is by conduction. In this situation one envisions an exchange of molecular energy from the hotter object to the cooler which is achieved only by contact. This method of heating is known to be relatively slow and consequently any important change in temperature can be achieved only by proper allowance for time. Our most familiar home heating devices are examples of conductive heating. These are the use of the hot water bottle, electric pad, warm water soaks or immersion in melted paraffin wax. In all such methods of heating the temperature of the heating agent must remain within safe levels, not exceeding 110 to 113° F., and as a general rule 30-minute applications are the minimum necessary for an adequate temperature increase of the area. Water is very advantageously used for heating because of its high specific heat, but more prolonged hyperemia can be obtained by melted paraffin. Electric pads avoid the difficulties of cooling but are less flexible in application and are not free of hazard from burn and shock.

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Another less familiar form of heating is by convection. By this we mean movement of warm currents of air or liquids. Although some hot air heating devices have been designed, these are so infrequently used that they warrant no detailed discussion. The penetration of heat to deeper tissues is again the same slow process as with conductive heating.

Increasing temperature by the use of radiant energy involves consideration of the factors of penetration and absorption of different wave lengths. As an increase in temperature is dependent on absorption of radiant energy, when the skin itself is the structure to be primarily heated, those wave lengths of radiant energy should be selected which are known to be absorbed by the skin. For this purpose infra-red generators should be used which emit primarily in the far infra-red range with a wave length greater than 1500 millimicrons. These invisible infra-red rays are absorbed completely by the skin and consequently cannot be considered as penetrating in spite of suggestive advertising to the contrary. Any depth heating effect is by the slow process of conduction from the warmed skin surfaces to the deeper layers of subcutaneous tissue. When heating is desired at a greater depth, it is more efficient to use the near infra-red rays from a luminous heat source, as a portion of this energy is transmitted through the skin to the subcutaneous levels where it is absorbed, so that penetration is more efficient and quick.

A fourth method of heating is by the conversion of high frequency electrical currents to heat, particularly the use of short wave diathermy. Even though these high frequency electrical currents can penetrate tissues to great depths, in the presence of normal circulation the skin is always heated at the same rate as the deep tissues and, in fact, the greatest heating effect occurs superficially which is desirable, as we rely on sensation of skin temperature to adjust dosage.

Sedative Effects. One of the commonest indications for the use of physical agents is for the relief of pain. Although the origin of the pain is only occasionally situated in the skin, the counter-irritant action of certain measures may have a sedative effect on deep seated pain. Experimental studies have shown that increase of skin temperature by one of the methods already mentioned is of some value in relieving pain from inflammatory processes in the skin. Cold also has a sedative action, but the alternate use of heat and cold has been found to be more efficient.[1] Another measure of known value as a counterirritant is histamine iontophoresis. In some cases an erythema produced by ultraviolet irradiation may relieve the pain of herpes zoster, although the mechanism is obscure. The pruritus of various skin conditions is also lessened occasionally by ultraviolet irradiation, but it must be used with caution as many acute processes are made worse.

Bactericidal Effects. The shorter wave lengths of ultraviolet radiation are known to have definite power to kill bacteria in the air and to a limited extent on surfaces. Experience has shown, however, that effective sterilization of skin for surgical purposes cannot be achieved safely with ultra-

violet irradiation. Any beneficial effects on pathogenic organisms in wounds or chronic ulcers are probably achieved secondarily through a stimulating effect on the tissues rather than by direct action on the bacteria. There is only limited experimental work available on the effect of radiant energy in wound healing. Clinical experience suggests that infra-red radiation alone or together with mild ultraviolet erythema production occasionally stimulates sluggish tissues in overcoming chronic infection and consequently hastens epithelial growth. The value of general ultraviolet irradiation for increasing general body resistance to infection is still controversial. Most controlled series of studies have dealt with the problem of the common cold and there is no conclusive value described, although some reports suggest a beneficial effect.[2, 3]

Pigmentation. Patients are frequently referred to physical therapy departments in order to acquire a so-called sun tan, but the patient more often than the physician is convinced of the desirability of such pigmentation. Mottled pigmentation can be produced by prolonged over-exposure to heat in any form and frequently follows home treatment. The even pigmentation following normal sunburn is produced in the skin in response to stimulation from ultraviolet radiation particularly of the longer wave lengths.[4]

Mercury, quartz, ultraviolet generators, although efficient in producing erythema, are not as effective in tanning as carbon arc or natural sunlight. Although there is little scientific proof of the value of general ultraviolet irradiation except in certain skin conditions, there can be no doubt of the frequent feeling of well-being associated with the appearance of ruddy health which comes from a good coat of tan, and the physician may wisely at times take advantage of this for psychological purposes alone. The actual prescription of ultraviolet should be in terms of the degree of erythema desired rather than in details of lamp distance and duration of exposure, unless the physician is familiar with the erythema capacity of the lamp to be used. Any properly trained technician can correctly adjust the exposure necessary to produce the result desired by the physician. Serious burns can result from prescriptions of ultraviolet given in terms of exposure time based on a lamp the doctor is familiar with, while the lamp the technician uses may be many times more powerful. I have frequently received prescription for three-minute exposures when the physician desired only an erythema dose, whereas such an exposure with our lamp would be twelve times the minimal erythema dose. Until an inexpensive and generally used meter is available, the erythema dose still remains the unit of measurement for ultraviolet radiation.

Circulation Increase. Most of the agents already mentioned serve to produce an increase in skin circulation as well as of the deeper tissues. It is well known that increase in temperature results in an opening of capillary beds, a more rapid arterial and venous flow, and in addition increased lymphatic drainage. Hyperemia is also produced by ultraviolet erythema and by iontophoresis. Massage too is capable of producing definite circulatory changes in the skin, even superficial stroking serving to open capil-

laries and more heavy stroking and friction producing a fairly prolonged hyperemia. It is probable that a large proportion of the beneficial effects of physical agents can be ascribed to the resultant increase in circulation.

Muscle

Temperature Elevation. The physical factors already mentioned in regard to heating the skin apply to increasing the temperature of muscles. The simplest method of heating is, of course, by conduction but, as already shown, this method is necessarily slow. It is more effective to have energy transmitted through the skin so that the heating effect may be relatively greater in the deeper tissues. Consequently the near infra-red from luminous heat sources is preferable to far infra-red generators. High frequency currents of diathermy have been shown to be the most efficient method of heating at a depth and should be used when this is desired.

Relaxation of Spasm. Muscle spasm is undesirable because of the resultant pain and the immobilization of joints which may lead to contracture. The mechanism of production of muscle spasm is not altogether clear, although one envisions a reflex arc through the spinal cord. If one accepts this explanation, it is reasonable to hypothesize reduction of spasm by the influence of heat with its known sedative effect upon sensory nerve endings, and clinical experience has shown this to be true. When very skilfully given, it is also possible to relax muscle spasm by massage, but the actual technic is so much an individual art that it is wisest to advise the technician to give massage for sedative effect and relief of muscle spasm rather than to indicate the details of technic. Muscle spasm can also be prevented or diminished by carefully guided active assisted exercises and by traction. Relaxation therapy may include special technics such as deep breathing and psychosuggestion. The spasticity from upper motor neurone disease, including the rigidity of Parkinson's disease, may be diminished by rhythmical exercises and special muscle reëducation technics. Occupational therapy is often prescribed to advantage in these cases.

Strengthening. Muscles with intact nerve supply can be strengthened only by active exercises graded in their resistance to produce some fatigue and consequent hypertrophy. In general, the therapist is more familiar with the specific exercises than the physician prescribing treatment, and it is sufficient in the prescription to indicate graded exercises for strengthening effect with precaution as necessary for range of motion and general limitations such as indicated by poor cardiac reserve.

Prevention of excessive atrophy following denervation can be achieved best by appropriate electrical stimulation. Although actual nerve regeneration cannot be changed by electrical stimulation, there is now a considerable body of experimental evidence to show that interrupted direct current stimulation of a frequency sufficient to cause tetanic contraction of the denervated muscle, repeated daily or even less often, enhances the speed of recovery once reinnervation occurs.

Stretching. One of the most frequent problems in the field of physical medicine is overcoming contractures of soft tissues including muscle. In most instances this is best achieved by active exercises under control of the patient rather than by passive stretching. Frequently mechanical devices and leverage effects are used, always under active muscle control. In the prescription it is usually adequate to order active stretching or very gentle passive stretching with the instruction that no pain, or only minimal pain, is to be produced. Further details may include suggestions as to the use of weights, pulleys, elastic traction, etc. Stretching is usually best achieved by the synergistic action of several agents, including heat, sedative massage, and finally exercises. Frequently optimum results are observed during immersion in warm water and with the mild massaging effect of whirlpool agitation. In this case the exercises are given simultaneously with the heat and massage.

Bones. The effect of physical agents on the metabolism of bones is only sketchily understood. The action of ultraviolet irradiation in the prevention of rickets is well known and needs no further discussion here. It is also generally conceded that oral use of vitamin D precludes the necessity of ultraviolet irradiation. The internist should remember, however, that in cases of impaired intestinal absorption calcium metabolism may be improved and tetany relieved by general irradiation with ultraviolet when oral medications are unsuccessful. That bone atrophy results from immobilization is well known and it is generally accepted, without the necessity of laboratory proof, that exercise is beneficial in preventing excessive atrophy in these instances. The exact rôle of deep heating particularly by diathermy in cases of fracture and delayed union still awaits more experimental investigation. The value of physical therapy in fractures cannot be overlooked, but it is of more interest to the surgeon than the internist.

Joints. Physical therapy and, in many cases, occupational therapy play an important rôle in the total treatment program of joint disease. As joints require motion for the maintenance of normal physiologic action, in the presence of inflammation and pain the proper amount of motion can best be obtained under the guidance of a trained physical therapist. It is usually essential to diminish pain and muscle spasm and this can be effectively accomplished in the majority of cases by judicious use of local heat, occasionally gentle, sedative massage, and guided active assisted exercises within a pain-free range. In the presence of pain associated with inflammatory joint disease, muscle atrophy and loss of normal control of movement are frequent findings. Such patients are benefited by skilled supervision in muscle re-education to prevent atrophy and to increase the strength which is necessary for maintenance of joint function. Active exercises are the rule in joint disease. Passive motion should be reserved for individual cases as selected by the specialist. There is no conclusive experimental evidence that heat of any sort, iontophoresis, ultraviolet irradiation, massage, or exercise has any specific effect on joint function except that which can be explained by

motion. There is a possible exception in that removal of effusion in joints can be speeded by massage and exercise, possibly also by deep heat. There is no evidence that inflammatory processes can be cured by these methods. Further details of prescription in the case of joint disease will be referred to later.

Intestines. Heat is frequently applied to the abdomen for pain of intestinal origin. There is evidence to support the belief that such applications diminish increased intestinal motility.[5] Although cold applied externally may be thought to diminish intestinal activity, experimental evidence suggests the opposite effect.[5] Symptomatic benefits of local heat in cases of intestinal pain should not be overlooked. Pain arising from other viscera, particularly the pelvic organs, may be reduced by deep heat as applied by means of short wave diathermy. These effects are probably produced by the increase in circulation secondary to changes in temperature gradients.

Metabolism. There are only a few recognized metabolic effects ascribed to the use of physical agents. The effect on calcium and phosphorus metabolism in the prevention of rickets in children by ultraviolet irradiation is outstanding. Systemic application of heat also generally increases oxidative processes. Exercise, too, increases heat production and may secondarily improve metabolism in various portions of the body. The effect of ultraviolet on metabolism, particularly immunological responses, is still to be determined by further investigation.

Peripheral Circulation. It has already been shown that the normal response to an increase in temperature of the skin and subcutaneous tissues is an increase in circulation. This involves dilatation of the capillary bed, increased rate of arterial blood flow, and improvement in venous and lymphatic return. Superficial capillary dilatation can also be achieved by massage and iontophoresis. Venous and lymphatic flow is improved by fairly heavy massage and, in addition, active muscle contraction. It should be remembered that this increase in circulation from the application of heat is due to reflex activity. When using high frequency electrical currents, generalized vascular responses are obtained if high dosage is used at the beginning of the application. This immediately increases the circulatory rate and dissipates the heating effect. Moderate dosage is accordingly advisable at the beginning of the application and only later increasing the total amount of electrical energy. It is also possible through reflex activity to increase the rate of blood flow in the extremities by the application of heat to distant parts such as the trunk or upper extremities. This method of relaxing vasospasm is safer in patients with impaired circulation where the increased metabolism resulting from direct application of heat may be dangerous.

The use of alternate hot and cold applications in cases of vasospasm is now generally recognized to be of little value, if not contraindicated. The use of mechanical suction and pressure apparatus is also thought to be of very limited usefulness in the majority of individuals with peripheral vas-

cular disease. Buerger exercises, although commonly prescribed and certainly not harmful, are, however, not of proved worth scientifically. They may still be used empirically and also the oscillating bed in selected cases for the same purpose.

Nerves. There is a large body of clinical evidence to indicate that painful impulses can be diminished by the application of heat to the surface. A few experiments have shown that heat and cold, or alternate use of both, have a definite sedative effect as well as other counter-irritant measures.[1]

The spasticity of muscles resulting from upper motor neurone disease as already mentioned can be favorably influenced by the use of heat, carefully used sedative massage, followed by a skilfully controlled exercise and training program.

In the case of supposed diminished activity of the neuro-muscular apparatus, massage is known to stimulate so that improved muscle tone results. Such massage can be used with advantage in cases of prolonged bed rest prior to mobilization. The stimulating effect of gentle massage in certain cases of psychiatric disorders is well recognized clinically, although the mechanism of its action is obscure. Hydrotherapeutic measures in psychiatric conditions are also accepted forms of treatment, but beyond the scope of this presentation.

Diagnosis

Having discussed briefly the scientific background of physical medicine, we may now proceed with some of the indications for its use and details of the prescription. Although with other forms of treatment it is generally conceded that diagnosis must be made before beneficial treatment can be anticipated, it is still commonly the practice to send patients with undiagnosed symptoms to physical therapy. If a physician in the field is consulted, it is then up to him to make the diagnosis and prescribe the treatment in detail. Otherwise the technician is too often left in the unfortunate position of having to decide the details of treatment for symptoms of unknown etiology. For the best results it is obvious that a working diagnosis should be provided in order that the physical therapy prescription may be intelligently utilized. There are frequent occasions, however, when response to physical therapeutic measures may aid in arriving at the ultimate diagnosis. This is a stimulating situation for the specialist in physical medicine and a diagnostic tool not to be overlooked by the internist. For example, the differential diagnosis of ruptured intervertebral disc, rheumatoid arthritis, and peripheral neuritis may frequently be made more clear by the response to physical therapy. Similarly, symptoms of mechanical origin in relation to the spinal column may be improved by remedial exercises, thus differentiating them from infectious processes. More specific instances of diagnostic methods in physical medicine have to do with electrical testing of nerves and muscles.

Choice of Physical Therapeutic Agents

After arriving at an understanding of the disturbed physiologic processes leading to symptoms in a given case and imparting this information to the physical therapist as a part of the prescription, the next problem is the choice of agents to be used. Instead of a routine order of baking and massage, with even a minimal background of information concerning the effects of physical agents as outlined, it is the duty of the physician to decide if increased temperature is desirable and, if so, either indicate which tissues should receive the increased heat or indicate the method of heating most suitable for this effect. Heat may occasionally be contraindicated or of no benefit and, if so, should be omitted from the prescription. The specific values of massage, for stimulation and also for sedative effects, should be kept in mind and the prescription should mention the effect desired when prescribing massage. When exercises are prescribed, it is best to indicate the result expected rather than mention simply active or passive exercises. If relaxation of spastic reflexes or muscle spasm is wished, exercises with that in view should be suggested and likewise exercises for strengthening, stretching, or improvement in muscle control, coördination, and balance. Further details of exercises can safely be left in the hands of a well trained technician by simply mentioning the precautions of pain, fatigue, etc. The duration of application of each agent, with the exception of ultraviolet irradiation, can be indicated within reasonable limits depending on the tolerance of the patient and reaction to treatment. Synergistic effects of a combination of measures should not be overlooked: passive means of increasing circulation by heat and massage can with advantage precede active measures such as exercise so that the total response is greater than the individual application of the agents separately.

The frequency of treatment is a matter of individual decision and includes evaluation of a variety of social, economic, and psychological factors as well as physiologic effects. When passive measures alone are used they must be repeated frequently, at least daily or more often. Treatment and supervision may be less frequent in cases where the patient can be instructed to participate at home in the use of heat, occasionally massage, and always in active exercises. It is always of importance to determine when the time has come to stop treatment. This can be done only by a proper evaluation of the effects, frequent examination by the therapist with adequate progress notes, and measurements by the physician. Every objective means possible should be employed for the purpose of evaluating the effect of treatment and determining when progress is no longer being achieved. The aid of occupational therapy should not be overlooked in encouraging the patient to acquire a more satisfactory adjustment to his disease and the treatment. In the presence of impairment of extremity function, it is prescribed for its remedial effect. It is frequently possible to accomplish more by skilfully guided crafts and shop work than by specified exercises. A well rounded

program of therapy includes proper coördination between physical and occupational therapy and gradation finally to occupational therapy alone as the last step toward free, unsupervised activity.

Indications for Physical Medicine

Joint Disease. Now that the general features of proper prescription of physical medicine have been discussed, we will mention briefly some of the definite indications for the use of physical and occupational therapy in medical conditions. Rheumatoid arthritis is an outstanding example of a medical condition in which physical measures are of value. In the patient confined to bed, training in body mechanics is essential, including recumbent postural exercises with progression to increased activity in the sitting and standing positions, with emphasis on proper mechanics in walking. To improve individual joint function a combination of physical measures is indicated, including thermotherapy, massage, splintage, and exercise. The choice of heat to increase local circulation is dependent somewhat on facilities available and frequent short applications are more desirable than occasional more prolonged and complicated measures. Efficiently applied, hot fomentations of 20 to 30 minutes three or four times daily, followed by an exercise period, are extremely useful. In some patients warm whirlpool baths or complete immersion in warm water make possible greater facility in exercise. Therapeutic pools may occasionally be utilized to advantage in teaching arthritic patients to walk. In general, a well organized exercise program is the single agent of utmost importance. Every patient should be taught correct methods of exercising involved joints so that damage is not done and all possible joint range maintained together with adequate muscle strength. All but the most severely crippled patients can be taught with proper supervision how to exercise their joints three to four times daily, with supervision only several times a week. In this disease which so frequently is chronic, more elaborate means of treatment are generally not indicated, for frequently repeated simple measures which can be used in the home are more desirable. The physical therapy program should be properly integrated with general medical care and orthopedic supervision. The intensity of measures, particularly exercise, should be regulated according to the general condition of the patient as suggested by symptoms, laboratory tests, and degree of muscle spasm. Mechanical aids should not be overlooked such as pulley apparatus, stationary bicycles, bed roller skates, and traction. Occupational therapy for psychological and functional effects should be included in the overall program of treatment. Frequently the occupational therapist may be of service in evaluation and pre-vocational training.

Physical therapy is also of definite value in the treatment of degenerative joint disease. Acute symptoms may be relieved by rest, local applications of heat, and gentle sedative massage. With subsidence of acute symptoms,

emphasis is then placed on strengthening of supporting musculature by carefully graded exercises. Whenever possible, postural defects should be remedied by stretching of slightly contracted soft tissues responsible for faulty posture and strengthening of improperly used and flabby musculature.

Physical therapy is especially recommended in cases of pain localized to periarticular structures, particularly individual muscles in the back, shoulder girdle, and neck areas. In these conditions, often called fibrositis, heavy massage including friction followed by light sedative massage, local use of heat, and corrective exercises may produce dramatic relief of symptoms.

The rôle of physical therapy in the treatment of infectious arthritis is secondary to specific measures when available. In those cases responding to chemotherapy, aside from the occasional use of heat for relief of pain, physical therapy is postponed until the infectious process is controlled. Mobilization may then be instigated with the aid of gentle massage and active guided exercises. In tuberculous arthritis the emphasis is, of course, on healing the process as a whole rather than an attempt to preserve individual joint function, so that heat, massage, and exercise are contraindicated. Carefully graded exposure to the sun according to standard technics, or general artificial ultraviolet irradiation, is used to improve general resistance. The occasional case of gonorrheal arthritis which is resistant to chemotherapy may be aided by artificial fever therapy in the fever cabinet. Such treatment is a highly specialized procedure, requiring expert technical skill and experience. It is to be undertaken only in hospitalized patients and by an experienced fever treatment staff.

There remain the large number of patients with symptoms referable to joints and supporting musculature, particularly in the region of the shoulder, back, and feet. In patients complaining of pain in the shoulder region, particularly when a localized area of tenderness is present, the diagnosis of bursitis is frequently made and physical therapy ordered. Perhaps the commonest prescription is for diathermy, either short wave technic or conventional long wave diathermy, the treatment averaging 30 to 40 minutes and repeated daily or on alternate days. Many cases of acute bursitis, however, do not respond favorably to diathermy, the stimulation to circulation apparently causing an increase in pain. These patients get more symptomatic relief from application of cold locally or a more superficial type of heating as with infra-red or luminous heat. Massage to the points of tenderness is usually contraindicated, although gentle sedative massage to surrounding muscles in spasm may be beneficial. Rest is of more importance than exercise in the early cases, but it is important to maintain a full range of motion by carefully guided active or active assisted exercises through the full range at least once daily. In cases of chronic adhesive bursitis, active and passive stretching may be added to the treatment prescription as soon as pain tolerance will allow. As the period of disability in these cases is long, it is wise to forewarn patients of this fact in order that they may persist in treatment. Physical therapy is often successfully combined with other

measures including irrigation with novocaine and saline, exploration and surgical removal of calcium deposits when present, or following manipulation for freeing of adhesions. In the shoulder where limitation of motion is so frequent after prolonged immobilization of muscle spasm, it is always wise to secure as much freedom from pain as possible by use of non-habit forming analgesics, particularly salicylates, in order that the patient may be able to perform exercises.

The problem of diagnosis and treatment of back pain is too complex to be discussed in any detail in this presentation. In the majority of cases a period of conservative treatment consisting in rest in bed with proper support to the back, analgesics and local use of heat for relief of pain, and sedative massage, when tolerated, is justifiable. Simple cases of mechanical back strain will respond to such treatment; probably also certain early cases of rheumatoid arthritis, and possibly some cases of protruding intervertebral disc. Pain having been relieved, the patient may then be gradually mobilized first with recumbent exercises for the low back, abdominal musculature and lower extremities; followed by posture instruction in the upright position and proper mechanical use of the back. Diathermy is a popular method of heating in these cases, probably with some justification because of the large amount of tissue to be heated in the back area.

Diseases of Blood-Forming Organs. Ultraviolet rays have been reported as favorably influencing some types of anemia. This effect is limited, nonspecific, and far less efficient than dietetic therapy and hematopoietic agents. Subacute combined degeneration of the spinal cord is a complication of pernicious anemia that often requires prolonged periods of muscle reëducation in addition to adequate replacement therapy during rehabilitation.

Endocrine and Metabolic Disorders. In a limited number of cases physical therapy is of value in diseases of the endocrine glands and in disorders of metabolism. In gout, because of its interference with joint function, some symptomatic relief may be obtained by physical means. Pain may be diminished by use of hot compresses and in some cases with cold applications and rest. During convalescence mild heat and graduated exercises aid in mobilizing the patient.

Exercise is known to improve sugar tolerance of diabetic patients when participated in to the proper degree. In the event of diabetic neuritis relief of pain is often achieved by careful administration of heat. In the event of pronounced muscular weakness, muscle reëducation in the form of specific strengthening exercises may be indicated.

Obese patients are frequently referred to physical therapy departments for weight reduction. Passive procedures, such as massage or vibration, however, are valueless. Heat treatments, such as cabinet baths or steam baths, temporarily reduce weight through dehydration but are not of permanent value. Caloric requirements may be increased by prescribed exercises but are successful only in combination with strict dietary control.

Pulmonary Disease. Although short wave diathermy has been used as an adjunct in the treatment of pneumonia and bronchitis particularly for

relief of pain, it is very rarely needed. Many patients with bronchial asthma are benefited by special breathing exercises. Postural exercises are indicated in the prevention and treatment of scoliosis secondary to lung abscesses, empyema, and thoracoplasty. In pulmonary tuberculosis heliotherapy is rarely indicated, although of benefit in extra-pulmonary complications such as involvement of bones, joints and the larynx. Graded convalescent exercises and occupational therapy have a definite place in rehabilitation of patients with tuberculosis.

Gastrointestinal Disease. Patients confined to bed for considerable periods of time because of peptic ulcer, ulcerative colitis, or other disorders of the gastrointestinal tract may be helped in their adjustment to the disease and hospitalization by diversional occupational therapy. Where psychological or emotional factors are important, the occupational therapist may be guided specifically by the psychiatrist interested in the patient. Physical therapy is not often needed, but pain from hypermotility of the intestinal tract may be diminished through the application of luminous heat or diathermy to the abdominal wall. Debilitated patients often respond with satisfaction to stimulating doses of general ultraviolet irradiation. Convalescent bed exercises may also speed recovery.

Heart Disease. The rehabilitation of many cardiac patients may be facilitated by suitable physical and occupational therapy. This consists in light gentle massage, followed by graded exercises or games and activities in the form of occupational therapy.

These are only a few of the conditions benefited by including physical medicine in the treatment regimen selected as illustrative examples.

Summary

In conclusion I should again like to emphasize the importance of the prescription in physical medicine. An adequate prescription should include: (1) a working diagnosis; (2) specific instructions as to choice of agents; (3) indication of effects to be produced; (4) statement of duration and frequency of treatment.

Such a prescription can be written by the internist with some knowledge of the scientific basis of physical medicine.

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BRONCHOPULMONARY ACTINOMYCOSIS *

By Earle B. Kay, M.D., *Cleveland, Ohio*

The presence of actinomyces in chronic bronchopulmonary infections is more common than it is generally considered to be. Interest in this subject was stimulated following isolation of the ray fungus in two patients with pulmonary suppuration. These patients required pulmonary resection in combination with chemotherapy to obtain cures.[1] Since then careful search for this organism has been made in similar patients. During the six-month period from May to November 1945, 240 patients were treated for chronic bronchopulmonary infections. Of these, 109 patients had *Actinomyces israeli* isolated (by direct examination and culture) from the sputum, and 65 from bronchoscopic specimens. The exudate aspirated from lung abscesses in six patients, and the drainage from sinus tracts in two patients with empyemas secondary to pulmonary suppuration were also found to contain actinomyces in combination with other organisms.

The 65 patients from whom actinomyces were cultured from bronchoscopic specimens included 37 with varying degrees of bronchiectasis and pneumonitis, eight with lung abscesses, five with pulmonary suppuration, five with aspiration pneumonia, and two with pulmonary suppuration distal to obstructing carcinomas. In eight additional patients the only apparent disease was chronic bronchitis. In no case was *Actinomyces israeli* found to the exclusion of other organisms. In a number of patients this fungus appeared to predominate, but usually other organisms such as streptococci, staphylococci, spirochetes and fusiform bacilli and other less common organisms, were also isolated.

It has been known for years that *Actinomyces bovis* (*israeli*) may be an inhabitant of the normal mouth. It has not been generally appreciated that this same organism may also be frequently found in bronchopulmonary infections. The source of such infections is undoubtedly the result of aspiration of mouth and pharyngeal exudates. The ciliary and peristaltic cleansing action of the normal bronchi in healthy individuals prevents such aspirated flora from assuming any clinical significance. When this physiological action is lost in patients with bronchopulmonary diseases such as bronchiectasis, the presence of mouth organisms deep in exudates can readily be explained. Actinomyces in infections such as pulmonary suppuration, chronic lung abscesses, and chronic pneumonitis result also from aspiration. In most instances they are of no clinical importance until anaerobic conditions occur. A blocked bronchus secondary to a plug of exudate would initiate such anaerobic conditions.

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The finding of actinomyces with such frequency originally caused considerable concern. Previous experience had related only to isolated cases. Was this an extraordinarily large series of bronchopulmonary actinomycosis, or should such patients be considered as cases of bronchopulmonary infection in which actinomyces, as well as other organisms, were isolated after careful bacteriological examinations? On what basis should pulmonary actinomycosis as a clinical entity be differentiated from pulmonary suppuration in which the ray fungus was only one of several organisms present?

It might be assumed that the term "pulmonary actinomycosis" should be applied only to those patients who have pulmonary suppuration associated with chest wall sinuses from which this organism can be isolated. However, it is known that pyogenic, as well as tuberculous infections, may also have draining sinuses secondary to underlying pleural and pulmonary involvement. The term "pulmonary actinomycosis" is then comparable to the terms "streptococcal," "staphylococcal," and "spirochetal" pneumonitis. There is no question that actinomyces under certain conditions may predispose to chronicity and as such may be partially responsible for the development of chronicity in bronchopulmonary infections.

Care was exercised to verify the identity of this supposedly pathogenic non acid-fast anaerobic ray fungus. With accumulated experience, it became apparent that the presence of actinomyces in bronchial and pulmonary exudates was a rather common occurrence and was not so significant clinically as had been originally thought. The clinical course and response to chemotherapeutic or surgical measures of patients with pulmonary suppuration did not appear to be influenced by the presence or absence of actinomyces. As is well known, pulmonary suppuration is a very chronic condition in itself.

At first additional precautions were followed when actinomyces were present. Increased dosages of sulfonamides and penicillin were employed preoperatively, if operations were to be performed, but this was later found to be unnecessary. Considerable discussion arose as to the advisability of performing operative procedures in the presence of actinomyces for fear of spreading the infection and the development of sinuses. Should a patient with actinomycotic pulmonary suppuration be continued on chemotherapeutic management instead of having operative therapy even though there had been no improvement? Would a chronic draining sinus follow drainage of an actinomycotic lung abscess, or would an actinomycotic empyema follow a lobectomy? The treatment of these patients, however, was not modified because of the presence of actinomyces. Operations were performed when indicated and in no instance was the post-operative course complicated by actinomycotic empyemas or draining sinuses. Actinomyces were isolated in the pleural fluid of one patient following pneumonectomy. The fluid promptly became sterile, however, with intrapleural injections of penicillin and sulfadiazine.

It is now felt that the presence of this organism is much less a factor

in the determination of the clinical course, chronicity, and prognosis of such infections than the mechanical factors of bronchial occlusion or drainage, tissue destruction, fibrosis, and avascularity. Patients with chronic bronchopulmonary infections in which these mechanical factors were present were just as resistant to conservative therapy as were those complicated by actinomyces.

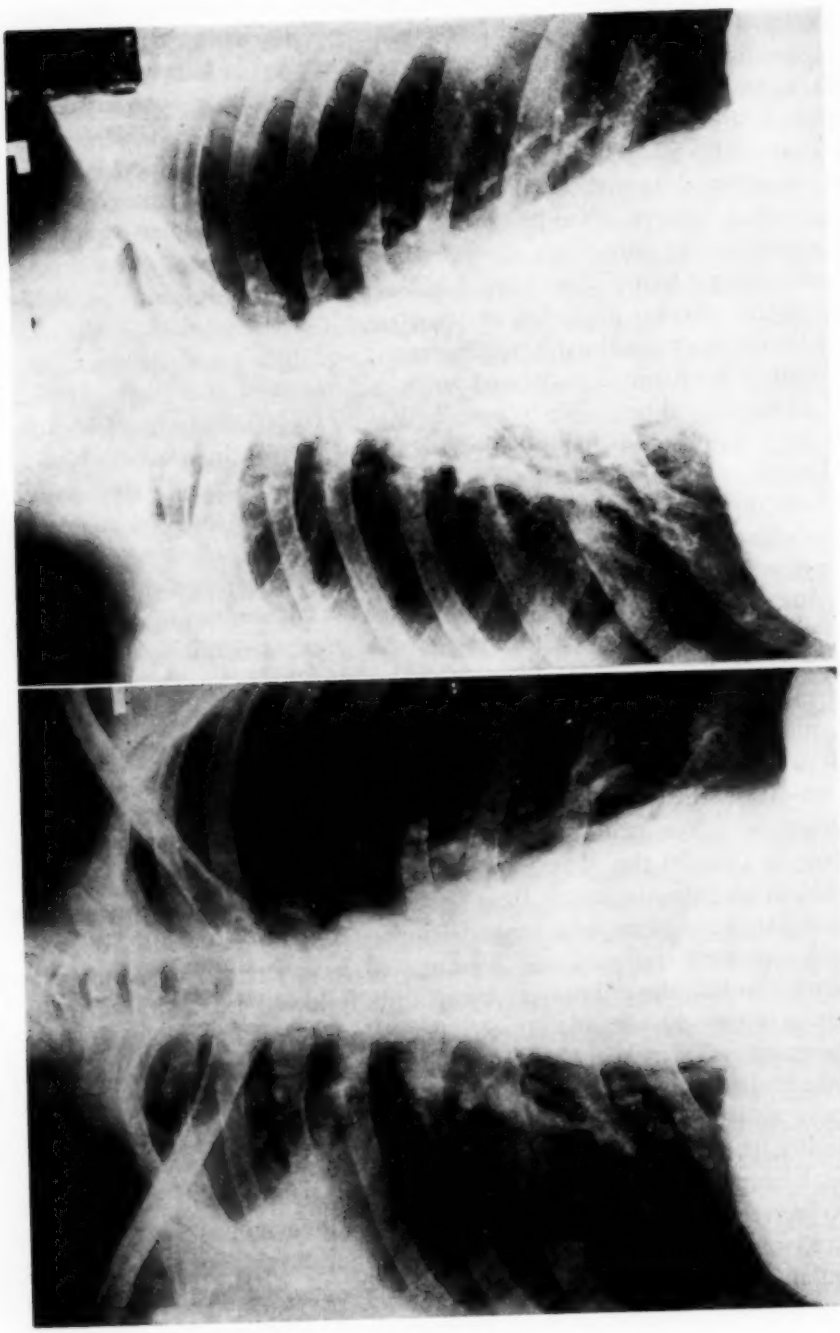
Approximately 50 per cent of the patients with bronchiectasis had actinomyces isolated bronchoscopically. There was nothing characteristic about this group except that the sputum appeared to be more copious in amount, more foul in odor, and more frequently bloody than when actinomyces were not present. The high incidence of bloody sputum probably results from the vascular granulation tissue seen in actinomycosis.

The patients with minimal bronchiectasis, and those with chronic, and with ulcerative bronchitis associated with actinomyces were all given a course of intratracheal penicillin[2] (usually 30,000 to 50,000 units of sodium penicillin in a saline suspension daily for a period of three weeks) with marked benefit. In most of these patients the chronic productive cough cleared markedly and in several the actinomyces could no longer be isolated from bronchoscopic specimens.

The patients with chronic bronchopulmonary infections, apart from those having bronchiectasis, chronic bronchitis, and suppuration distal to obstructing carcinomas will be discussed with greater detail. Only those 20 patients from whom actinomyces were isolated bronchoscopically from bronchial exudates or from chest wall sinuses will be considered. Actinomyces in addition to other organisms were isolated in approximately 50 per cent of all patients having chronic lung abscesses and pulmonary suppuration.

The onset of the pulmonary infection was frequently insidious and characterized by a low-grade fever at first that later became septic, a productive cough, pain in the chest, and increasing debility. Bloody sputum was present in all patients at one time or another. The clinical course was characterized by remissions and exacerbations. The onset usually followed episodes of exposure, fatigue, and weight loss associated with combat or military life. In two the pulmonary complaints followed extraction of teeth, and in three upper respiratory infections. Poor oral hygiene had been present in many and was still poor at the time of admission to this hospital. The disease had usually been present for three to six months and in several for over a year prior to the patients' admission. For the most part they had been treated with varying dosages of penicillin and sulfonamides.

Physical examination revealed undernourished, debilitated patients with a foul productive cough. The oral hygiene was invariably poor. Actinomyces were isolated in most instances from tonsillar crypts, from about dirty gums, and in several cases from periapical abscesses. Chest wall sinuses were present in two patients. The pulmonary involvement was unilateral in 15 and bilateral in five patients. Percussion of the lung fields showed dullness to flatness over the involved sites. The breath sounds were usually



B

A

FIG. 1. Pneumonitis (A) which cleared following a six-week course of intramuscular penicillin therapy. Actinomyces was the predominant organism in both the sputum and bronchial exudate.

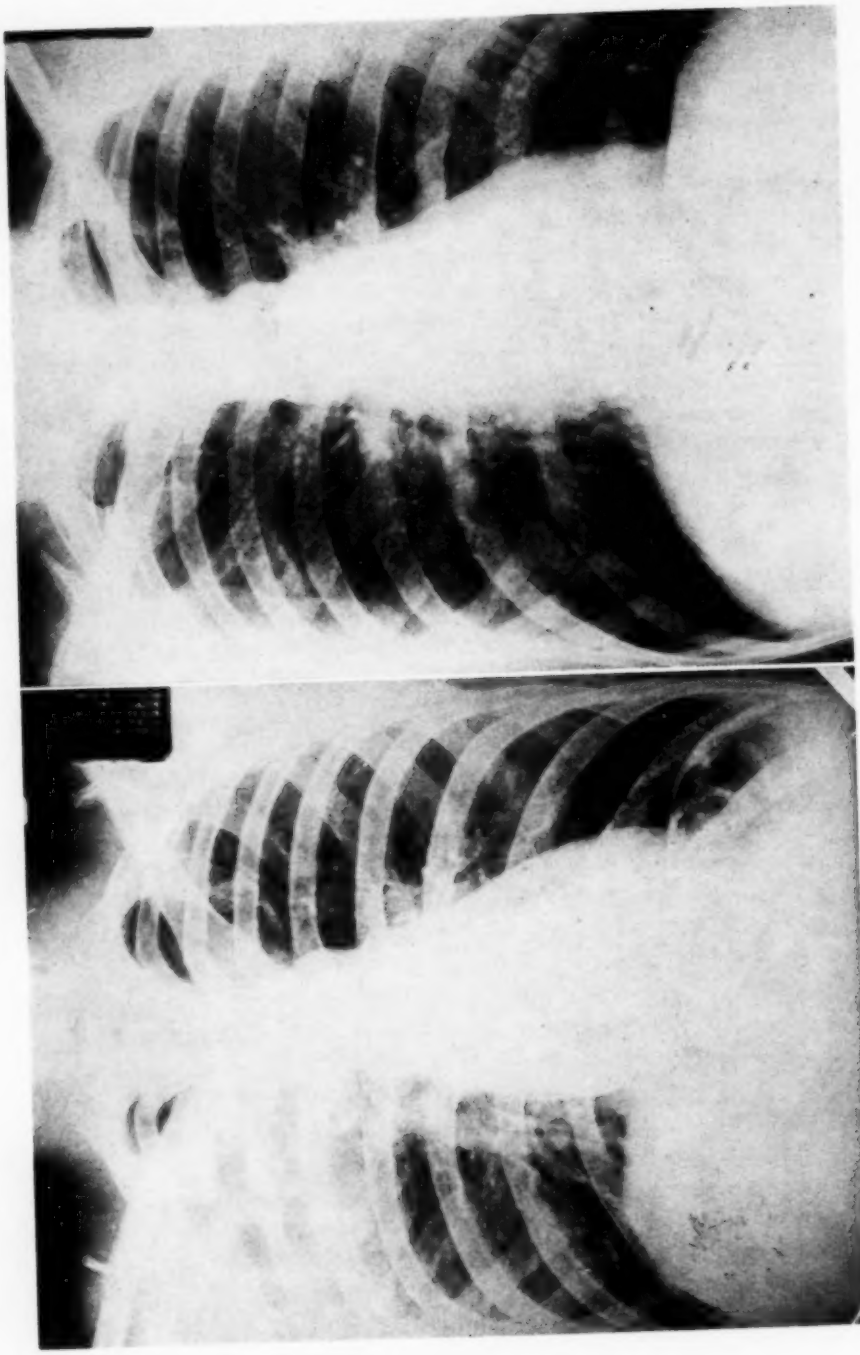
decreased or bronchial in character. Occasionally amphoric breath sounds were present over areas of cavitation. Moist râles could always be heard. The mid lung field appeared most commonly involved and particularly on the right side. The mid lung field was involved in 10 instances, the upper in seven and the lower in three.

The bronchoscopic appearance of the tracheobronchial tree in these infections was not specific. In some instances the bronchial mucous membrane appeared more hyperemic, granular, and inflamed than usually noted. As much exudate as possible was collected in a bronchoscopic container at the time of bronchoscopy and immediately sent to the laboratory for bacteriological examinations. It was a routine request that all bronchial exudates be carefully studied for fungi and sufficient exudate was supplied to allow adequate examinations. The sputum in these patients varied between one to three ounces daily, was usually yellowish and frequently blood-tinged. Sulfur granules could be seen on direct examination in approximately one-fourth of the specimens. Microscopic identification from the smear was possible in 13 of the 20 cases and in all cases the actinomyces grew on culture. It was of interest to note that gastric washes from two patients were also positive for actinomyces. The presence of actinomyces was usually verified on at least four or five repeated examinations.

The clinical course and response to treatment of patients with chronic pneumonitis, lung abscesses and pulmonary suppuration appeared to depend largely on the chronicity and severity of the infection. All patients were again placed on large doses of penicillin, a combination of penicillin and sulfadiazine, or sulfadiazine alone in an attempt to determine the efficacy of these medications. Though the infection appeared to respond to each of these three methods, penicillin, or penicillin in combination with sulfadiazine appeared most effective. It is essential in such cases that penicillin and sulfadiazine be given in large doses and continued for a long time in spite of roentgen clearing and clinical improvement, otherwise recurrence will take place. Such infections are very resistant to therapy and tend to recur. The dosage of penicillin employed consisted of 50,000 units of penicillin intramuscularly every three hours for 8 to 12 weeks and in some cases even longer. A blood level of 10 milligrams per cent of sulfadiazine was maintained. Preliminary evidence from in vitro experiments suggests that streptomycin is more effective than either penicillin or sulfonamides in inhibiting the growth of actinomyces, but sufficient evidence has not been accumulated for a report at this time.

Those patients (five) with roentgen evidence of pneumonitis without evidence of cavitation who appeared to have good bronchial drainage (figure 1) responded excellently to penicillin and sulfadiazine therapy. All of these patients had had their disease for from three to five months. Large doses of penicillin either alone or in combination with sulfadiazine were again administered for a period of 8 to 12 weeks. Three of these have healed completely and have remained healed for over three to four months. A

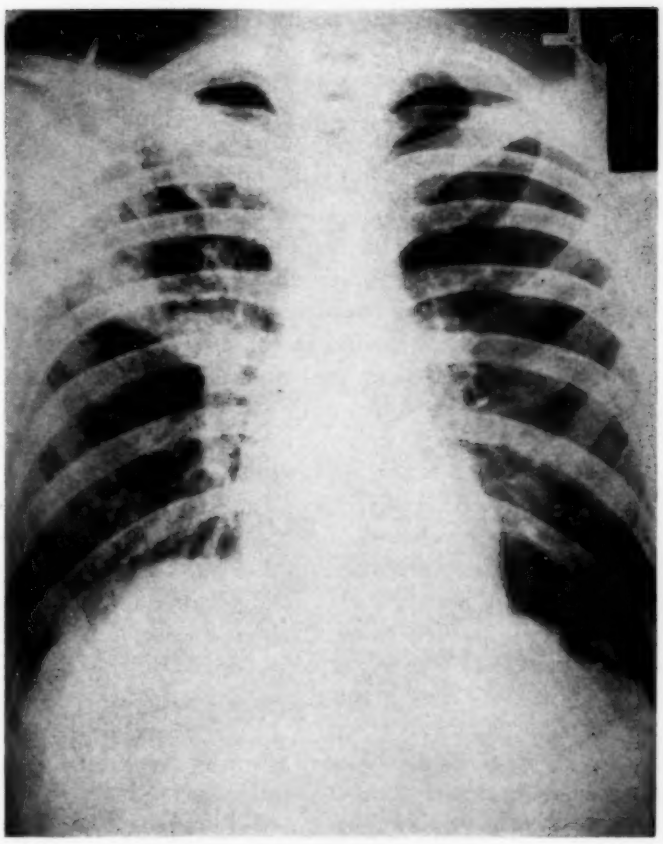
FIG. 1. Pneumonitis (A) which cleared following a six-week course of intramuscular penicillin therapy. Actinomyces was the predominant organism in both the sputum and bronchial exudate.



B

A

FIG. 2.



C

FIG. 2. Pneumonitis (A) which showed marked clearing following a two-month course of penicillin and sulfadiazine therapy (B), but which recurred soon after this therapy was discontinued (C).

fourth has considerable residual pleural scarring. The fifth patient healed almost completely, but the infection recurred after the penicillin was discontinued. Since this time there has been practically no response to chemotherapeutic measures and surgical treatment will probably be necessary (figure 2).

If cavitation were present (figure 3), less benefit from chemotherapeutic and antibiotic therapy resulted. The general symptoms of toxicity were allayed and there was marked symptomatic improvement. This was frequently associated with roentgen clearing of the pneumonitis surrounding the cavitation. In only one patient did the abscess heal on conservative measures alone. Three patients healed following surgical drainage in conjunction with penicillin or sulfadiazine. One patient following drainage continues to have residual pneumonitis and a draining sinus. Two other patients noted partial improvement following drainage but pneumonitis and cavitation persisted and resection of the diseased tissue by lobectomy was

required. In no instance was the postoperative course complicated by actinomycotic involvement.

In more extensive cases of pulmonary suppuration (figure 4), similar response to conservative measures was noted. Pneumonectomy was necessary in two patients before healing occurred and resection of the diseased tissue by lobectomy was performed in two other instances. Both of the latter cases had previously had drainages of lung abscesses with only partial benefit. Four of the six patients having pulmonary resections were treated postoperatively with sulfadiazine in combination with penicillin and the other two with penicillin alone. Two patients have now been well for over a year, the others except one for a period of three to eight months. It is too soon after operation to evaluate one patient but his condition to date (six weeks) is satisfactory. In the remaining patients it is felt that resection of the diseased tissue will also be necessary before healing will take place.

The involved pulmonary tissue at operation appeared to be markedly consolidated and fibrotic. Extensive pleural adhesions and symphyses were present in five of the six patients operated upon. The pulmonary fissures were obliterated by adhesions and inflammatory tissue necessitating in several instances transection between clamps. Examination of the surgical specimen again showed marked fibrosis about multiple necrotic and burrowing abscesses, the walls of which were covered by dirty, grayish-appearing granulation tissue. The actinomyces was readily isolated from these abscesses in each case.

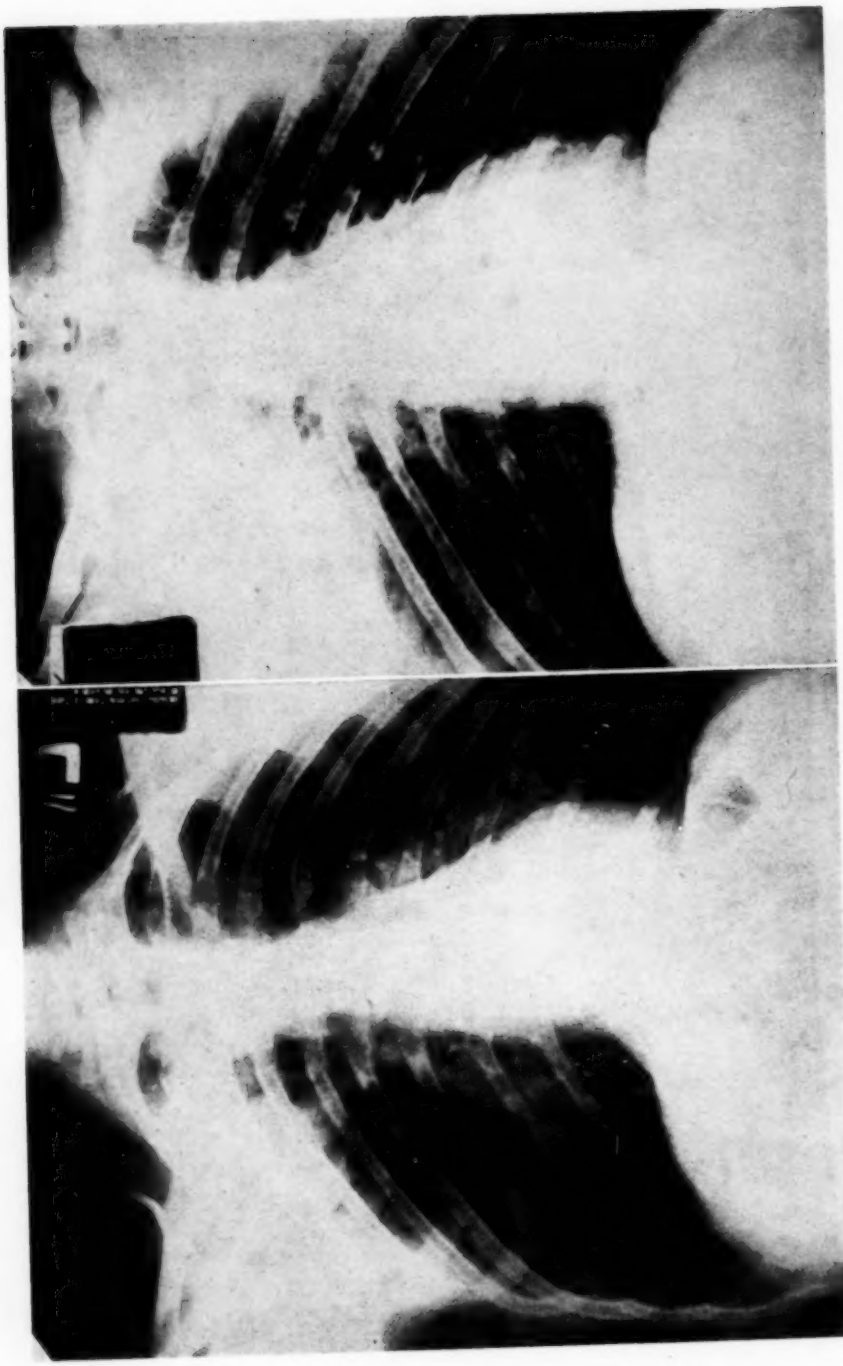
One patient with draining chest wall sinuses secondary to pulmonary and pleural involvement healed after a four-week course of sulfadiazine (figure 5). After approximately five months a lumbar abscess developed which has required multiple drainages. Evidence of infection is still present. A second patient with multiple rib involvement drains intermittently.

Summary

Actinomyces israeli is commonly found in chronic bronchopulmonary infections. Careful examinations in 240 patients treated over a six-month period revealed that 109 of these patients had this organism present in sputum specimens, 65 of these patients also had this organism isolated from bronchial exudates obtained bronchoscopically. In approximately 50 per cent of the patients treated who had bronchiectasis, aspiration pneumonia, lung abscesses, and pulmonary suppuration, the actinomyces was isolated in addition to other organisms. It is felt that the presence of the ray fungus is less of a factor in influencing the clinical course, response to treatment, and prognosis of chronic bronchopulmonary infections than the mechanical factors of bronchial occlusion, tissue destruction, avascularity, and fibrosis. It is debatable as to whether such cases should be classified as pulmonary actinomycosis or rather as aspiration pneumonia, lung abscesses, or pulmonary suppuration in which this fungus is present.

A B

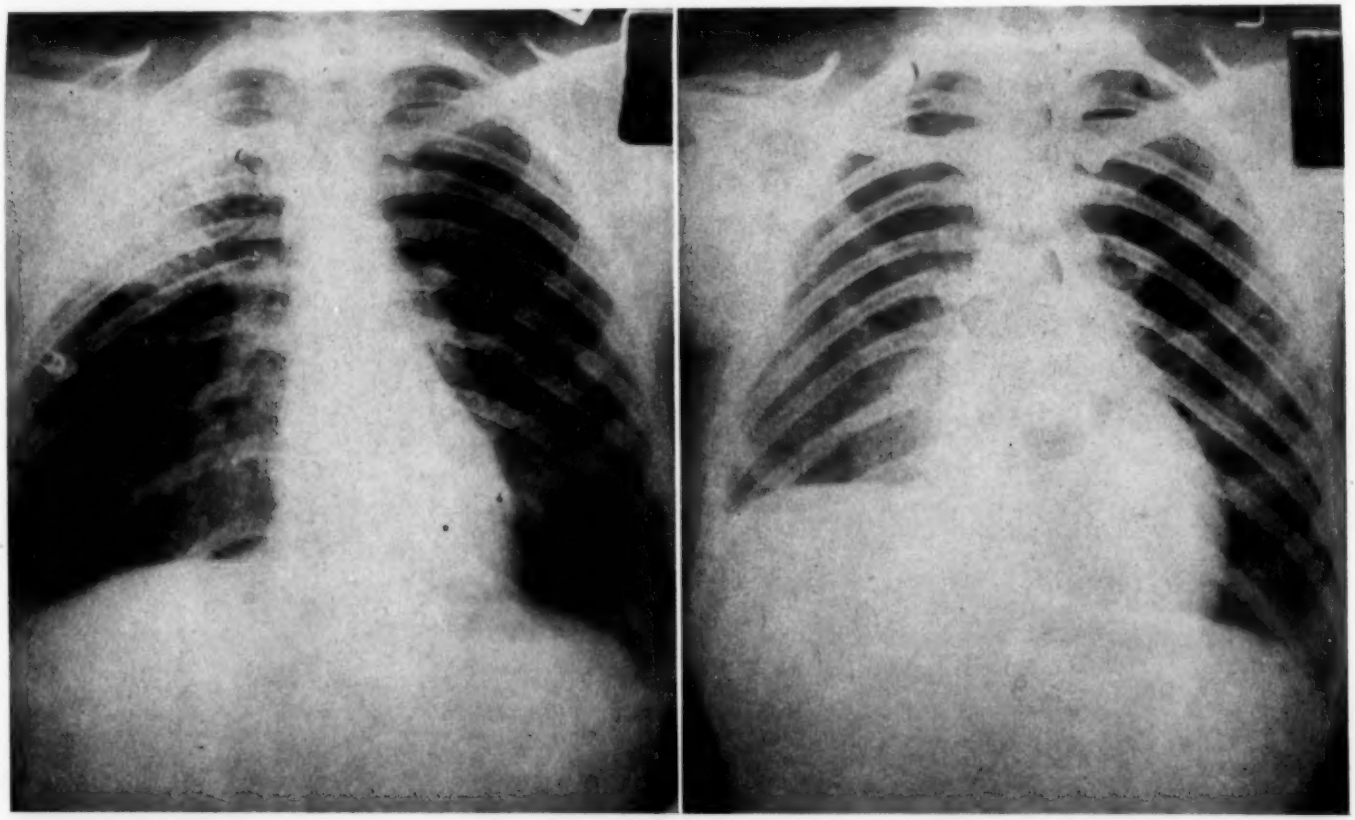
FIG. 3. Lung abscess of six months' duration (A) which had shown no response to chemotherapy or antibiotics. Culture of the abscess at time of drainage showed the actinomyces to be one of the predominant organisms present. (B) Roentgenogram taken six weeks following drainage.



B

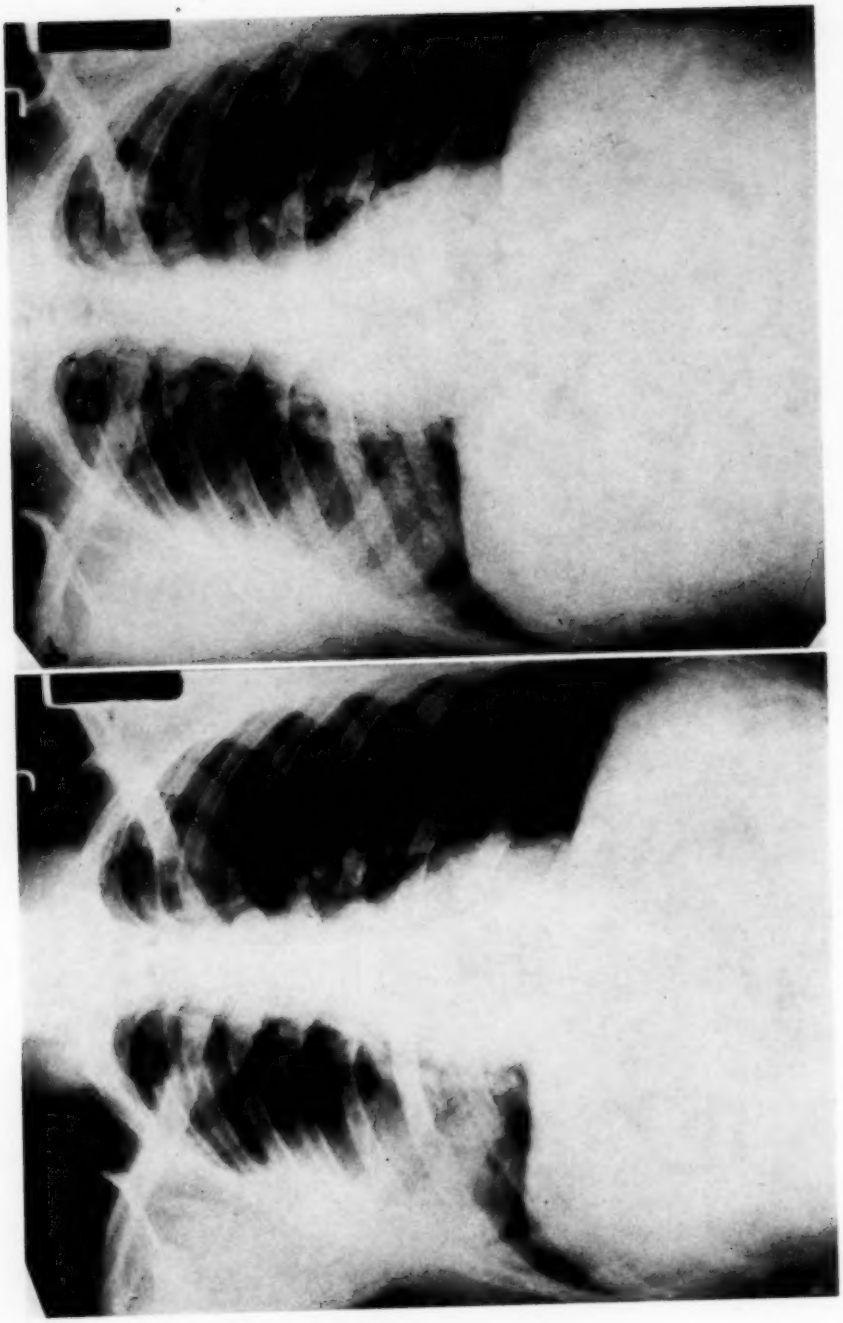
A

FIG. 4.



C D

FIG. 4. Pulmonary suppuration of eight months' duration (A). The lesion was progressive during repeated courses of penicillin and sulfadiazine therapy (B). Evidence of suppuration persisted following drainage (C). Cure obtained following resection of the upper lobe (D). Actinomyces cultured from the abscesses in the surgical specimen.



B

A

FIG. 5.

C

FIG. 5. Pneumonitis and pleural thickening (A) associated with draining chest wall sinuses (C), which healed following aspiration and a four-week course of sulfadiazine therapy (B).

It was not felt that the presence of the actinomyces influenced significantly the clinical course or that there was any significant difference from other patients in whom the actinomyces were not present. It is realized that *Actinomyces israeli* is an anaerobic organism and under such conditions may predispose to chronicity, and in turn may be partially responsible for the development of chronicity in such infections, but this is also true in varying degrees of other organisms also isolated. All patients were treated similarly without particular reference to this fungus. Operations were performed when indicated and in no patient was actinomyces responsible for any post-operative complication. Apparent cures have now resulted following pneumonectomy in two patients and lobectomy in four patients. Three other patients having abscesses were cured by surgical drainage alone. A discussion of the clinical course and response to both conservative and operative therapy in these patients is presented.

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CASE REPORTS

BANTI'S SYNDROME WITH MULTIPLE ANEURYSMS AND THROMBOSES OF THE SPLENIC BLOOD VESSELS *

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CONFUSION still exists concerning the pathogenesis and pathologic picture of the disease complex called Banti's syndrome. Two opposing views are held concerning its development. Banti [2] and his adherents considered the splenomegaly to be the primary cause, with liver and vascular changes occurring secondarily. The opposing concept, recently given favor, holds the splenic changes to be secondary to some other cause, usually chronic passive congestion within the portal system. An obstruction is usually described either in the liver, the intra-hepatic blood vessels,[1] the portal circulation or the splenic vein itself.

Banti,[2] in his original descriptions, pointed out that endophlebitis of the splenic, portal and hepatic veins was a part of the pathologic picture but secondary to the splenic disease. Warthin [3] supported the opposing concept in his presentation of cases showing portal vein obstruction as the dominant feature. However, he was unable to reproduce splenomegaly experimentally by ligation of the splenic vein in animals. McMichael [4] introduced "portal hypertension" to explain the pathologic changes seen in the portal vein by comparing their similarity to those seen in arterial hypertension. The recent work of Rousselot [5] Thompson,[6] and Larrabee [7] has advanced "congestive splenomegaly" as the basic condition resulting from hypertension in the portal vein. The obstructive factor causing congestion may be intra-hepatic in the form of cirrhosis, or extra-hepatic in the form of thrombosis, stenosis, external pressure on the vein, congenital malformation or cavernous transformation of the vessel. Of the 65 cases studied by Rousselot 60 per cent showed one of the above causes. In the remaining group an undetermined obstructive factor was postulated.

In addition to sclerosis of the splenic vein, enlargement, tortuosity and varicosities have been repeatedly described. However, less attention has been paid to similar changes which may occur in the splenic artery, as aneurysms, despite the fact that some 100 such cases have been reported by various authors, usually as an incidental finding at autopsy and independent of splenomegaly. Aneurysm of the splenic artery is relatively uncommon, occurring, according to various reports, once in 1500 cases. It may be either single or multiple, saccular or cirsoid. Several cases have been cited in which splenomegaly associated with Banti's syndrome has been attributed to the aneurysm. Lossen [9] in 1904 reported such a case in a 24 year old female who had splenomegaly with a cirsoid aneurysm of the splenic artery. The splenic vein also showed varicosities. Liver changes were minimal. Baumgartner and Thomas [8] reported a similar case in which

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they considered that the aneurysm, by causing pressure on the splenic vein, resulted in splenic congestion. A similar case was reported by Rudnev.[10] Sanford and Dolly [11] in 1905 described a case in which tortuosity and thrombosis of the splenic vein and a dilated and tortuous splenic artery were considered to be the cause of the splenomegaly. In 1942 Trimble and Hill [12] reported a case in which stenosis of the portal vein and multiple aneurysms of the splenic artery were found. There was no cirrhosis. A review of the literature indicates that enlargement of the splenic artery or vein is not uncommon with splenomegaly. Thus, in the cases of aneurysm of the splenic artery reviewed by Baumgartner and Thomas [8] and Remizov,[13] about half of the cases showed splenomegaly. In a case described by LeFevre and Pettis [14] splenomegaly was diagnosed about three years prior to rupture of the aneurysm. Guy in 1938 reported two similar cases. Whereas some authors believe that the splenic artery aneurysms antecede the splenomegaly, it must also be considered that the arterial changes may be secondary to the splenomegaly.

Few cases of Banti's disease have been reported in recent years in which profound vascular changes were found both in the splenic artery and vein. We are reporting such a case because of its pathologic interest and the possibilities of its interpretation in view of the more recent concepts of the disease.

Case Report

A 30 year old white male of Mediterranean extraction was admitted to the U. S. Marine Hospital, Chicago, on July 10, 1944, complaining of an enlarged spleen. He stated he had been in good health until March 10, 1944, when he suddenly became ill with abdominal pain, nausea and vomiting, requiring morphine for relief. He was hospitalized in Belfast, Ireland, and later transferred to a hospital in Scotland where examination revealed an enlarged spleen, the cause of which apparently was not determined. At the time of admission to this hospital he had no complaints except for discomfort due to the enlarged spleen.

The patient's past history is of interest in that he was born in Armenia during the first World War (1915). His family was frequently near starvation and their diet remained deficient until they came to this country in 1922. He had one brother who died of tuberculosis two years after coming to this country.

Physical examination revealed a well developed and well nourished white male who did not appear acutely ill. The spleen extended down to a level just above the umbilicus, was smooth, non-tender. The liver was barely palpable on deep inspiration below the right costal margin.

Laboratory studies showed 4,990,000 red blood cells per cu. mm., 15 grams hemoglobin per 100 c.c. blood, 6,800 white blood cells per cu. mm., with a differential of 26 per cent lymphocytes, 5 per cent monocytes, 57 per cent neutrophiles, and 12 per cent stab cells. Blood Wassermann and Kahn tests were negative. Urine was negative. Sedimentation rate was normal. Platelet count was 124,000 per cu. mm. Thick and thin smears for malaria were negative on numerous occasions. Blood culture for *Leishmania donovani* was negative. Tuberculin test was reported positive. Agglutinations for brucellosis were negative in all dilutions. The euglobulin precipitation test for kala-azar was slightly positive but the aldehyde and antimony tests were negative. Total protein was 7.01 grams per 100 c.c. of serum; albumin 5.03, globulin 1.98 grams per 100 c.c. A roentgenogram of the abdomen showed "a very large spleen, the lower border of which reached almost to the iliac crest."

Operation on August 3 revealed an enlarged spleen and a small, atrophic, fibrotic liver with multiple nodules typical of cirrhosis and consistent with Banti's syndrome. The immediate post-operative condition was satisfactory but on the second post-operative day there was a rise in temperature to 105° F. and the patient became irrational, developed evidence of peritonitis, and died on the sixteenth post-operative day.

Autopsy Findings

The body was that of a youthful male of Mediterranean extraction. The abdomen was distended due to a diffuse peritonitis. The spleen had been previously removed surgically. The liver was small, weighing 1140 grams, with a hobnail surface, and on section it was found to be firm, irregularly fibrosed and greenish-orange-yellow in color. The kidneys showed cloudy swelling. The gastrointestinal tract was intact. No varicosities were found in the esophagus. The superficial blood vessels of the stomach were not engorged. The portal vein was of the usual caliber and

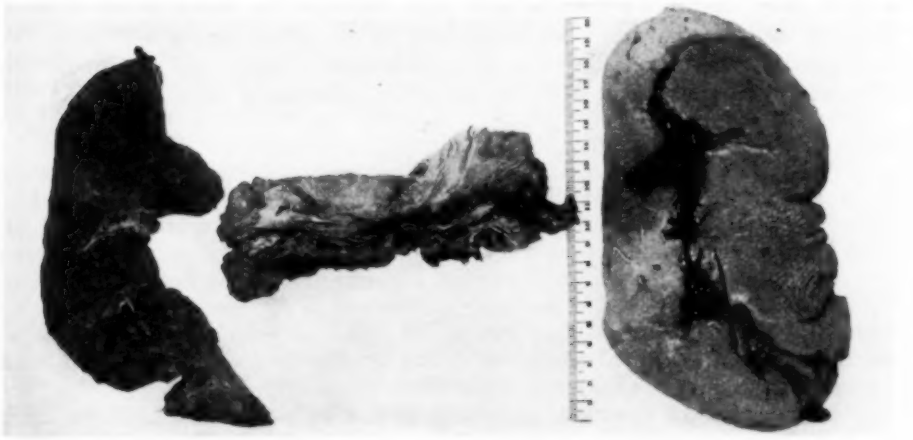

Fig. 1. The cirrhotic liver, varicose splenic vein, tortuosity of splenic artery and splenomegaly.

thin walled. The splenic vein was considerably altered (figures 1 and 2). Near the tail of the pancreas, just before the vessel entered the spleen, it was stenosed over an area of 1.5 cm. so that the circumference was reduced to 4 mm., completely obliterating the lumen. This narrowing was due to dense thickening and fibrosis of the wall. Immediately proximal to this occlusion, overlying the body of the pancreas, there was a varicose dilatation of the vessel producing a sac measuring 4.5 by 6.5 cm. Two smaller sacs filled with recent thrombi, one measuring 3 cm. and the other 2 cm., projected from the larger one. The remaining portion of the splenic vein was dilated (25 mm. in circumference), and thin walled. The splenic artery was tortuous, thickened, and formed multiple, cirsoid, telescoping aneurysms. Several smaller saccular aneurysms containing antemortem thrombi projected from the main artery. The wall averaged 25 mm. in circumference, showed atheromatous deposits upon the intima and was thickened. The spleen, which had been previously removed, was considerably enlarged weighing 750 grams and measuring 20 by 11 cm. after fixation in formaldehyde. The capsule was thickened and on section the surface was found to be bloody but the consistency of the organ was firm.

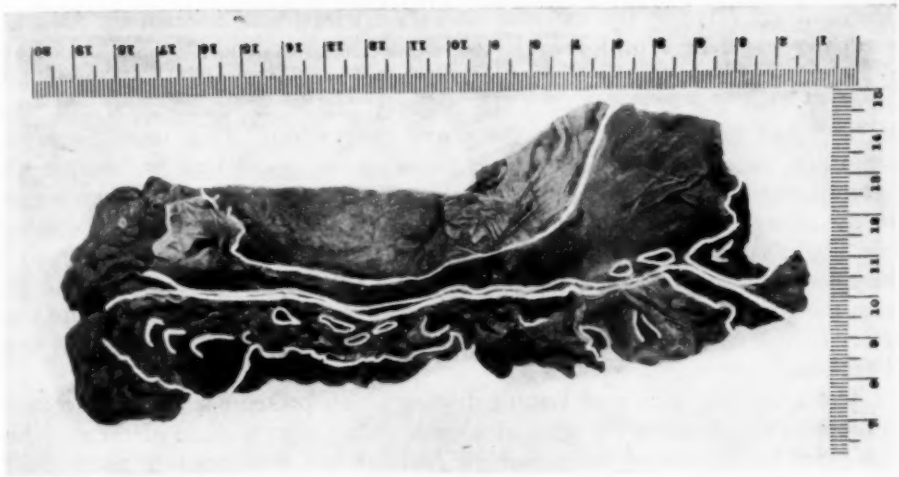

FIG. 2. Splenic blood vessels viewed from posterior. Upper vessel is splenic vein and portal vein. Arrow points to the stenosis and immediately distal to it is the varix and smaller sacs. Lower vessel is the dilated, tortuous artery with multiple small aneurysms.

Microscopically the liver showed the findings encountered in a Laennec type of cirrhosis and the spleen showed "fibroadenie" and the other changes described by Banti. The wall of the splenic vein was fibrosed and hyalinized. At the site of the stenosis, in addition to these alterations, calcification was also present. The splenic artery showed considerable thickening of the muscularis with increase of connective tissue.

DISCUSSION

One cannot, from the pathologic findings, draw any conclusions concerning the course of disease in this case. However, it is interesting to consider the possibilities involved. According to Banti's concept the splenomegaly would be the initiating factor. An unknown toxin would damage the splenic vessels and finally involve the liver. Proof of a toxin capable of doing this is lacking in this case as in others reported. Stenosis of the splenic vein, according to Rousselot and others, could initiate a congestive splenomegaly in which case the liver cirrhosis would be entirely coincidental. The aneurysms of the splenic artery might be considered as spontaneous and a cause of pressure upon the splenic vein. However, there is no indication that the aneurysms encroached upon the vein or anteceded the other described changes. Cases cited in the literature in which aneurysms of the splenic artery have been considered capable of such pressure on the splenic vein are not convincing. Because the stenosis of the splenic vein anatomically was found to be of long standing, Warthin's [3] concept might be applied in this case. Accordingly, the obstructive changes of the splenic vein would be primary, the splenomegaly would be the result of congestion. The interpretation of this case which best explains all the findings would attach primary importance to the cirrhosis. Recent work points to nutritional deficiencies as important etiological factors in cirrhosis. Of particular significance in this case is the fact that the patient was Armenian and in his

childhood subjected to the extreme starvation which was inflicted on these unfortunate people in World War I. Whether this starvation was sufficient and of long enough standing to instigate a cirrhosis is problematical. Nevertheless, assuming that the cirrhosis was the primary factor, a splenomegaly of some degree could be expected from the portal congestion. This same congestion might also cause sufficient sclerotic changes in the vessel wall to produce ultimately a stenosis. The additional obstruction thus produced might then account for the advanced splenomegaly seen in this case. The varicosities of the splenic vein might result from hypertension proximal to the obstruction. Fibrosis of the spleen and splenic vein could then demand a sufficient increase in blood flow from the arterial side to result in atheromatous changes such as are found in any arterial hypertension. Aneurysmal formations could be the sequelae of these alterations.

Thus, we have a case of Banti's disease which presents a complete complex of findings which are in the form of a circle rather than a chain of events. One may point to any one of the pathologic findings and incriminate it as the initial cause. It has been presented because of its widespread ramifications rather than in an attempt to prove any one factor as responsible for Banti's syndrome.

Summary

A case of Banti's syndrome has been presented which demonstrates cirrhosis of the liver, splenomegaly, thrombosis, varicosities and dilatation of the splenic vein, and multiple aneurysms and tortuosity of the splenic artery. The various possible explanations for this complex have been considered. The case emphasizes the profound changes which may occur in the splenic circulation in this disease.

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WATERHOUSE–FRIDERICHSEN SYNDROME: RECOVERY FROM SHOCK IN FATAL CASE *

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INTRODUCTION

THE dramatic and usually fatal sudden circulatory collapse appearing in cases of fulminating septicemia (usually meningococcic) associated with adrenal hemorrhage has been most commonly recognized under the name Waterhouse-Friderichsen syndrome. The recognition and delineation of this condition has followed the course of most of the diseases which have yielded to clinical elucidation. First only scattered cases were reported and compared. Then as the condition became more widely known, it was more commonly recognized so that of the approximately 175 cases now in literature, over half were reported in the last five years.[1] Most of these have been in children although at least 40 cases in adults have also been recorded.[1] Increasingly, now, attempts are being made to classify cases according to various clinical and pathological criteria and to trace the pathogenesis of the disease. This, in turn, is leading to a rational approach to therapy.

The somewhat diversified concepts of the pathogenesis of this condition which have been presented in recent reports may be briefly synthesized as follows. A primary bacteremia develops with the usual manifestations of an acute febrile illness. The bacterial infection overwhelms the primary hematogenous defenses and in some cases bacterial growth is so rapid that phagocytized meningococci may be seen within leukocytes in direct smears of the peripheral blood.[2] Various manifestations of severe damage to the vascular system then appear; the most important of these are medical shock and hemorrhages of the adrenals, skin and other sites. Since hemoconcentration apparently does not occur and blood loss is relatively insignificant, the profound medical shock is probably due to generalized vasodilatation. This is manifested peripherally by striking variegated cyanosis. It is in the shock phase that most cases succumb. Heroic therapeutic measures are necessary to compensate for the disparity between the circulating blood volume and the dilated peripheral vascular bed.

In several reports [3-6] the importance of shock has been emphasized and the

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From U. S. Marine Hospital, Pittsburgh 24, Pennsylvania.

adrenal damage has been considered to be secondary and coincidental. It has been shown by Williams [7] and emphasized by others [8] that death may supervene in meningococcemia with the classical clinical picture of shock and purpura but without adrenal hemorrhages. According to this concept, even a case with adrenal hemorrhages should be considered primarily as a bacteremia and its designation as a case of Waterhouse-Friderichsen syndrome on the basis of minor adrenal hemorrhages becomes a matter of etymological quibbling. On the other hand, there are cases in which extensive adrenal damage has occurred and it is important to attempt to determine its clinical effect. The vasopressor function of the adrenal cortex is now widely recognized. Rich [9] has pointed out that in experimental animals and in cases of Addison's disease, adrenal cortical deficiency is aggravated very rapidly by acute infections. Weil and Brown [10] have demonstrated an increased urinary excretion of cortin-like elements during acute infections.

Adrenal damage due to causes other than hemorrhage has been reported in acute infections with the clinical picture of Waterhouse-Friderichsen syndrome. Rich [9] reported cortical cellular necrosis with the conversion of the solid cords of cells into tubular structures. Banks and McCartney [11] described cases of thrombotic necrosis of the adrenals and of focal adrenalitis.

All of these pathologic changes in the adrenals must contribute to the severity of the medical shock which, in most cases, is directly responsible for death. The chances for recovery from shock are decreased by adrenal damage. This distinction is important in evaluating the cases of recovery from the Waterhouse-Friderichsen syndrome which have been reported recently.[12-16] In very few of these cases was clinical evidence of adrenal damage demonstrated following recovery from the acute phase of the illness. That recovery from the shock phase of this disease even in the presence of adrenal damage can occur has also been demonstrated by Marangoni and D'Agati [17, 18] who had two cases who recovered from shock only to die subsequently with severe toxic damage to the liver and kidneys in addition to adrenal hemorrhages.

The purpose of this paper is to report a case similar to those of Marangoni and D'Agati.

Case Report

The patient was a 43 pear old white riverboat engineer whose final admission to the hospital was on January 9, 1945, at 9:05 a.m.

Family history was noncontributory.

He had had five previous admissions since 1937 with the following diagnoses: lung abscess of right lower lobe, common cold, pneumonia, pleurisy of left side, and otitis media. The recovery from each of these conditions was considered good. In 1944 he had three attacks of acute febrile illnesses thought to be pneumonia for which he was hospitalized elsewhere with a prompt recovery. Twenty-four hours before his final admission he developed chills, fever, abdominal pain, vomiting, and severe headache. These symptoms progressed rapidly until he became irrational and then semicomatose during the night before admission.

Physical examination showed a semicomatose, apathetic white male with ashen-gray facies lying quietly in bed responding resentfully and in monosyllables to questioning. Temperature was 35.5° C. Blood pressure was 70 mm. Hg systolic and 50 mm. diastolic. The pulse was 84 per minute and the heart sounds were faint. The mucosa and skin showed evidences of marked dehydration. Scattered over the

entire body surface were many small petechiae ranging from the size of a pinhead to one-half inch in diameter. A few crepitant râles were heard in the axillae but otherwise the lungs were normal. Slight right epigastric tenderness was present. Minimal pitting edema of the legs was noted. Neurological examination on admission was negative except for questionably positive Kernig and Brudzinski signs and within a few hours both of these tests became markedly positive.

Laboratory studies on admission were reported as follows: leukocytes 44,500 per cu. cm. with 90 per cent neutrophiles and 10 per cent lymphocytes; erythrocytes 4,530,000 per cu. cm.; hemoglobin 77 per cent; blood sugar 232 mg. per cent; nonprotein nitrogen 43 mg. per cent; creatinine 2.6 mg. per cent; malaria smear negative; smear of blood from petechia on right ankle contained gram-negative diplococci within leukocytes; spinal fluid contained 44,000 leukocytes per cu. cm. and smears showed intracellular gram-negative diplococci; blood culture was positive for meningococci.

A spinal puncture was performed soon after admission. The spinal fluid was cloudy with a pressure of 310 mm. of H_2O and a normal Queckenstedt response. One hundred thousand units of penicillin were introduced intrathecally. The patient was also given 5 gm. of sodium sulfathiazole and another 100,000 units of penicillin intravenously. He then received 15,000 units of penicillin every three hours intramuscularly and 1 gm. of sulfadiazine every four hours. Eschatin 1 c.c. was given intramuscularly every four hours and an almost constant flow of intravenous fluids was maintained.

Eight hours after admission the patient was definitely out of shock; he was quiet but still somewhat incoherent. The temperature had risen to 38° C. (axillary). The pulse was 88 per minute, respirations 26 per minute, and the blood pressure 135 mm. Hg systolic and 60 mm. diastolic. Fourteen hours after admission his temperature had risen to 40.5° C. (axillary), the pulse was 120 per minute, and the respirations 40 per minute with a definite Cheyne Stokes pattern. He was profoundly comatose. About this time he developed gross and microscopic hematuria and was incontinent. In spite of continued therapy his condition became steadily worse and he died 24 hours after his admission and 48 hours after the onset of his illness.

Postmortem examination was performed seven hours after death; permission to examine the head was not obtained. Gross examination revealed the following positive findings. Petechiae ranging from 1 mm. to 8 mm. were found in the conjunctivae and skin especially around the ankles. The lungs were extremely congested and edematous having a uniform dark red color with thin sero-sanguineous fluid oozing from the cut surfaces. Several bronchiectatic dilatations were noticed in the right lower lobe. The heart appeared dilated with a soft, flabby, dull brown myocardium. Scattered over the epicardium were many petechiae. The parenchyma of the liver, spleen, and kidney was soft and apparently congested. Scattered through the renal parenchyma were reddish spots resembling hemorrhages. The left adrenal was somewhat enlarged but the right was approximately normal in size. The cortico-medullary boundaries were sharply defined. Scattered through the cortices and especially at the cortico-medullary boundaries were numerous areas of hemorrhagic degeneration measuring 1 to 3 mm. in diameter.

Microscopic examination showed the following significant positive findings.

Lung: The alveolar walls were moderately thickened with dilatation and congestion of the capillaries and extensive extravasation of blood and edema fluid into the interstitial tissues and into some alveoli. Other alveoli were air containing. The pleura was moderately thickened and its capillaries were congested.

Heart: The myocardium contained occasional small focal aggregations of neutrophiles and some muscle bundles had a fibrillar appearance with loss of staining quality. Neutrophiles were also scattered along the endocardium and at one place neutrophiles

and fibroblasts had collected to form a small mass projecting into the ventricle. All blood vessels were dilated and one showed intimal proliferation.

Liver: Most of the blood vessels and especially the central veins were distended with blood. Moderate fat was seen in the central zones of the lobules and a slight increase in the lymphocytes in the spaces was noted.

Spleen: The architecture was normal except for the presence of erythrocytic congestion and a scattering of neutrophiles in the red pulp.

Kidney: The glomeruli appeared generally swollen. This was noted both in the capillary tufts and the epithelial linings, but the tuft capillaries were not unusually congested. At several points Bowman's capsules contained finely fibrillar, noncellular exudate. Occasional tubules contained blood and the tubular epithelium as a whole showed degenerative changes. The vessels generally were blood-filled and the larger arteries showed slight, irregular endothelial proliferation.

Adrenals: The sinusoids and capillaries were extremely congested. Many hemorrhagic areas were scattered throughout the cortex, especially in the zona fasciculata and zona reticulata. In these areas of hemorrhage there was disruption of the cellular architecture. Most of the cortical cells showed vacuolation and irregular staining of their cytoplasm and pyknosis or pale hyalinization of their nuclei. In the zona glomerulosa there were several discrete foci of polymorphonuclear infiltration in areas of partial or complete cellular destruction lying between the sinusoids. A careful search of specially stained slides failed to reveal any bacteria.

Discussion

This case is presented as another example of recovery from shock in a case of Waterhouse-Friderichsen syndrome with an eventually fatal termination. It again demonstrates that with vigorous therapy these patients may recover from the shock phase of the syndrome, thus supporting the claims of those authors whose cases have gone on to final and complete recovery. It further shows that there is a second critical period in the recovery from this condition which is caused by damage to other organs especially the liver and kidneys (as shown by Marangoni and D'Agati [17, 18]) and also the lung, heart, and other viscera. Perhaps an important factor is the damage to the brain as pointed out by Banks and McCartney [11] in their "encephalitic" group of cases. Unfortunately we were unable to demonstrate this. This damage occurs not only because of the acute "toxic" action of the infectious agent, but also because of tissue anoxemia occurring as a result of impaired circulation during the shock phase of the disease.

As to the pathogenesis of the adrenal damage we would like to point out in this case the presence of "focal adrenalitis" in addition to hemorrhages. The localization of these areas suggests that hemorrhage may be secondary to damage to the adrenal cortical cells which form the walls of the sinusoids.

Summary

A case of Waterhouse-Friderichsen syndrome in an adult has been presented. This patient lived for almost 48 hours after the onset of his illness; he recovered from the primary shock phase of his illness only to die in the febrile and toxic secondary phase.

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FATALITY IN A BLOOD DONOR; A CASE REPORT, WITH A REVIEW OF THE LITERATURE*

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The American Red Cross through its Blood Donor Centers collected approximately 13 million pints of blood during the period between 1941 and 1945. At the Chicago Blood Donor Center approximately 640,000 pints of blood were collected in the three and a half years of its operation.

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On each donor a history was taken and a brief physical examination was made so as not to accept a donor with an acute infection or serious chronic illness. Many donors, however, withheld or denied information relative to their physical condition, so that they would not be rejected.

There has occurred only one fatality in a blood donor at any of the American Red Cross blood donor centers or any mobile unit station during this entire project. This fatality is presented.

Case Report

A white male, age 43, weight 55 kg., height 160 cm., presented himself for his fifth blood donation. All the donor requirements were fulfilled. There were no technical difficulties encountered during the venesection, and 500 c.c. of blood were readily obtained by the gravity method. No pumping or suction of any kind was used during the entire venesection. A few minutes after the completion of the venesection the donor had a small watery emesis and presented the usual systemic reaction that was observed in about 6 per cent of the donors.[1] The donor was examined by a physician who ordered him moved to the Recovery Room where atropine sulfate gr. 1/150 was administered hypodermically. At this time the blood pressure was 90 mm. of Hg systolic and 60 mm. diastolic; the pulse rate 78, and of moderately good quality. The blood pressure prior to bleeding was 120 systolic and 80 diastolic. A short time later the donor was allowed to sit up on the edge of the bed since he stated that he felt "better." After sitting up several minutes he stated that he now felt "weak," and again was ordered to recline. The blood pressure recorded at this time was 90 systolic and 60 diastolic and the pulse rate was 70. The donor seemed to improve with the change of position when he suddenly complained of slight substernal pressure without radiation, gasped several times and suddenly died. An ampoule of coramine followed by caffeine sodium benzoate (7½ grains) was administered subcutaneously immediately during the "gasping" period.

Past Medical History. The donor had made four previous donations of 500 c.c. each without any consequences. The last donation was made eight months previously. The donor's wife later stated that about one month prior to the last donation the donor had experienced substernal pain of short duration but did not seek any medical care at that time. He did not admit the above history of substernal pain at the admission examination prior to the donation. No history of previous fainting or known sensitivity to any drugs was obtained at any time. Clinical impression as to cause of death: Acute myocardial infarction due to acute coronary occlusion.

Autopsy *

An autopsy was performed several hours post mortem, and the conditions observed were as follows:

Chest: The pleural cavities were free of fluid. The lungs were moderately distended, purple gray and subcrepitant. On cut surface they were moderately moist with frothy fluid. Heart: The pericardial sac contained a few c.c. of clear fluid. The myocardium was soft and purple gray. The valves were unchanged. The aorta smooth throughout. Coronary arteries: The left circumflex artery was smooth and thin walled. The left descending branch had at a point 2 cm. from its origin a hyaline thickening 1 cm. long with a slight calcification. In the middle of this thickening the lumen was narrowed to pin-point size and would not admit the finest scissors.

* Dr. Victor Levine, pathologist for the Cook County (Ill.) Coroner, performed the autopsy and furnished the Autopsy Report.

The right coronary had, at a point 3 cm. from its origin, a hyaline and calcified thickening 1.6 cm. long. In the first centimeter of this thickening the lumen was irregularly ulcerated and occluded by a loosely adherent purple gray blood clot 7 mm. long. Just beyond this occlusion, but still within the region of the thickening the lumen was markedly narrowed to pin-point size and would not admit the finest scissors. Beyond the narrowed portions of both coronaries, the lumen widened out to normal and the walls were thin and smooth. On the posterior wall of the right ventricle there was an indistinct zone 5 cm. in width in which the cut surface of the myocardium showed scattered gray, firm areas 1 to 2 mm. in diameter of early fibrosis. The intervening muscle had a slight brown discoloration but no solid single infarcted area could be definitely demarcated.

Abdomen: The liver weighed 1500 gm., and was distended, fairly firm and purple brown. The spleen weighed 150 gm., and was fairly firm and deep purple. The kidneys weighed about 300 gm. together, and were dark purple gray with fairly distinct vascular marking on the cut surfaces. In the other abdominal organs nothing of note was observed.

Anatomic Diagnosis. 1. Thrombotic occlusion of right coronary artery. 2. Marked coronary sclerosis with narrowing of both the left descending and the right coronary arteries. 3. Focal fibrosis of posterior wall of right ventricle. 4. Edema of lungs. 5. Acute passive congestion of liver, spleen and kidneys.

Discussion

Death occurring during or immediately after blood donation is very infrequent, and is seldom reported in the literature when it does occur. A review of the literature was made to ascertain the cause of death in blood donors.

Since a possible contributing factor in coronary occlusion may be the slowing of the systemic circulation, and since the coronary flow is regulated by the mean level of the arterial pressure,[2, 3] especially the diastolic pressure, any marked fall in blood pressure may act as a precipitating cause of coronary thrombosis.

Approximately 6 per cent of the blood donors at the Chicago Blood Donor Center developed a systemic reaction [1] varying from slight to marked pallor, weakness, faintness, sweating, nausea and vomiting, with a transient drop in blood pressure. That the above symptoms occur during the drop in blood pressure has been demonstrated by Engel [4] and his coworkers, who further felt that in vasodepressor syncope provoked by venepuncture the primary reaction was a fall in blood pressure.

In the presence of coronary sclerosis there is a tendency to hypersensitivity of the vagal type of carotid sinus reflex.[5] It should be pointed out that the numerous emergency functions and the reserve capacity of the normal cardiovascular system enables a normal person readily to recover from a "faint," but derangements in the circulatory dynamics in an already damaged cardiovascular system which is unable to cope with a sudden drop in blood pressure may lead to the so-called "fatal" syncope.[5]

Masters [6] felt that regardless of whether coronary thrombosis took place on an arteriosclerotic basis or as a result of hemorrhage into a plaque, it could be attributable to alterations in the coronary circulation. These changes could be in blood volume, pressure and speed of flow within the arteries or changes in the physical and chemical properties of the blood. That such changes may occur following "syncope," i.e., transient drop in blood pressure with reduction of the

venous return to the heart [7] and diminished cardiac output which in turn result in decrease in speed and volume of coronary flow, is well established.

Nathanson,[8] in reviewing 142 autopsies showing occlusive coronary disease in which sudden death occurred, stated that death was explained on a "physiological" basis. In his report the preponderance of evidence indicated that cardiac standstill was the basis of temporary cardiac syncope, and ventricular fibrillation was the mechanism underlying the fatal syncope or sudden death of coronary disease.

Englehardt and Sodeman [9] have discussed syncope on exertion and its relationship to coronary artery disease with possible resultant occlusion of the right coronary artery which may interfere with the circulation to the Bundle of His and so cause various degrees of heart-block.

Cookson [10] in 200 proved cases of myocardial infarction pointed out that syncopal symptoms were present in 15 of these cases. In 10 cases the myocardial infarction was ushered in by syncopal symptoms. Vomiting was almost invariably present in the syncopal cases. In his series the prognosis for the cardiac infarction with syncopal onset seemed to be more serious than usual. At the onset of the myocardial infarction associated with syncope the appearance of the patient was that of severe peripheral circulatory failure often combined with a slow heart rate. Substernal pain was slight or absent.

Boyton and Taylor [11] in their report from the Blood Donor Service of The American Red Cross, which was dated as of April, 1944, and represented experience with approximately three and one-half million donors, stated that no death attributable to cardiovascular causes had occurred in any Blood Donor Center or at any Mobile Unit Station. In their report there were 10 deaths which occurred 48 hours after donation. In five cases a history of cardiovascular disease had existed but had been denied by the donor at the preliminary examination. Of the 10 fatal cases, seven were males, and three females. One donor was a seven time donor. The clinical diagnoses were probable coronary thrombosis in eight cases, and cerebral hemorrhage in two. In the single case in which an autopsy was performed the anatomic diagnosis was coronary sclerosis with acute cardiac dilation. In seven of the eight cases in which the clinical diagnosis of coronary thrombosis was made, death had occurred within four to eight hours after donation. Boyton and Taylor felt that these fatalities were actually coincidental and unrelated to the donation and that the normal expectancy for cardiovascular accidents of this nature is far greater than the experience of the Blood Donor Centers, regardless as to whether or not the factor of selection was considered.

Browne [12] reported a death in a male blood donor, age not stated, and it was felt that death was due to the injection of a large quantity of air into the vein at the onset of the venesection. An autopsy performed failed to show conclusively the cause of death.

In an editorial in the British Medical Journal [13] of August 1941 there was mentioned a death in a blood donor resulting from air embolism in which the use of an electric rotary suction pump described by Biddle and Langley became impaired during the venesection allowing air to enter the circulatory system. This case was not fully reported.

Simpson [14] reported that during a 10 year period, 1932 to 1942, there were

56 fatal cases of air embolism examined for medico-legal purposes, and that death during venesection accounted for four of these cases. No further details concerning these four cases were mentioned.

Montgomery [15] discussed the cause of death of a professional blood donor occurring 29 days after donation. The autopsy revealed multiple emboli, i.e. cerebral, mesenteric, and splenic.

Hines and Kessler,[16] in their study of 58 cases in which either the electrocardiographic or postmortem findings were those of coronary thrombosis, found that only 8 per cent of these cases had a red blood count lower than 4.5 million, and only 16 per cent had a hemoglobin less than 13 grams. In their series only two of the 58 cases of coronary thrombosis had an erythrocyte count less than 4 million. They also noted that there was a diminished clotting time and shortened prothrombin time in patients with high erythrocyte counts, and showed that similiar changes in clotting mechanism had been observed in patients known to have thrombosis at various sites. Hines and Kessler were able to lower the erythrocyte count and the hemoglobin level by repeated small venesections. On the basis of their experience with a small series of cases they felt that repeated venesections of small amounts was a rational treatment for the prevention and treatment of coronary thrombosis.

Summary

A review of the literature reveals that the reported causes of death in blood donors were either air embolism or cardiovascular lesions such as coronary thrombosis, cerebral hemorrhage, or other arterial emboli. A case is presented in whom postmortem examination revealed marked coronary sclerosis and narrowing of both the left and the right coronary arteries with myocardial lesions of variable duration prior to the venesection.

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FATAL SPONTANEOUS HEMOPNEUMOTHORAX: REVIEW OF THE LITERATURE AND REPORT OF A CASE *

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SPONTANEOUS hemopneumothorax in the absence of active tuberculosis is relatively uncommon. Hartzell [1] in 1942, in an excellent review of the subject, found only 40 cases in the literature and added three of his own. Fatal hemorrhage in spontaneous pneumothorax is even more rare. We have been able to find only 13 such instances on record that were confirmed by necropsy. Moreover, in these patients, postmortem examination not infrequently failed to reveal the origin of the lethal bleeding.

Because of the apparent rarity of fatal cases and since only four of them were studied microscopically, we felt that the report of an additional case might reemphasize and perhaps assist in clarifying certain obscure features in the pathogenesis of this disease.

CASE REPORT

A Lieutenant Commander in the Navy, aged 30, had always been well until five days prior to admission to the hospital, when he experienced pain in the left supraclavicular region after slinging a heavy bag over his left shoulder. Following this he had no particular symptoms until 2 a.m. on the morning of admission to the hospital, when he had a sudden severe pain throughout the left chest accompanied by weakness and difficulty in breathing. He was first seen by a civilian physician at 9:30 a.m., who advised immediate hospitalization. He was admitted to the hospital on a stretcher at 11 a.m. and, on examination, was found to be in profound shock and extreme respiratory distress. There was limited excursion of the left chest and on percussion it was hyperresonant, except for increased dullness at the base. The right chest was normal. The breath sounds were absent over the left chest and the heart and trachea were displaced markedly to the right. Heart sounds were heard to the right of the sternum which were regular but muffled. The pulse was very rapid and almost imperceptible and the blood pressure could not be obtained. He was given morphine and placed in an oxygen tent, and a total of 1000 c.c. of blood plasma was administered over a period of three hours. Roentgenogram of the chest revealed complete collapse of the left lung and fluid in the pleural cavity. Five hundred c.c. of blood were aspirated from the left chest cavity. The patient became comfortable, his respiratory distress

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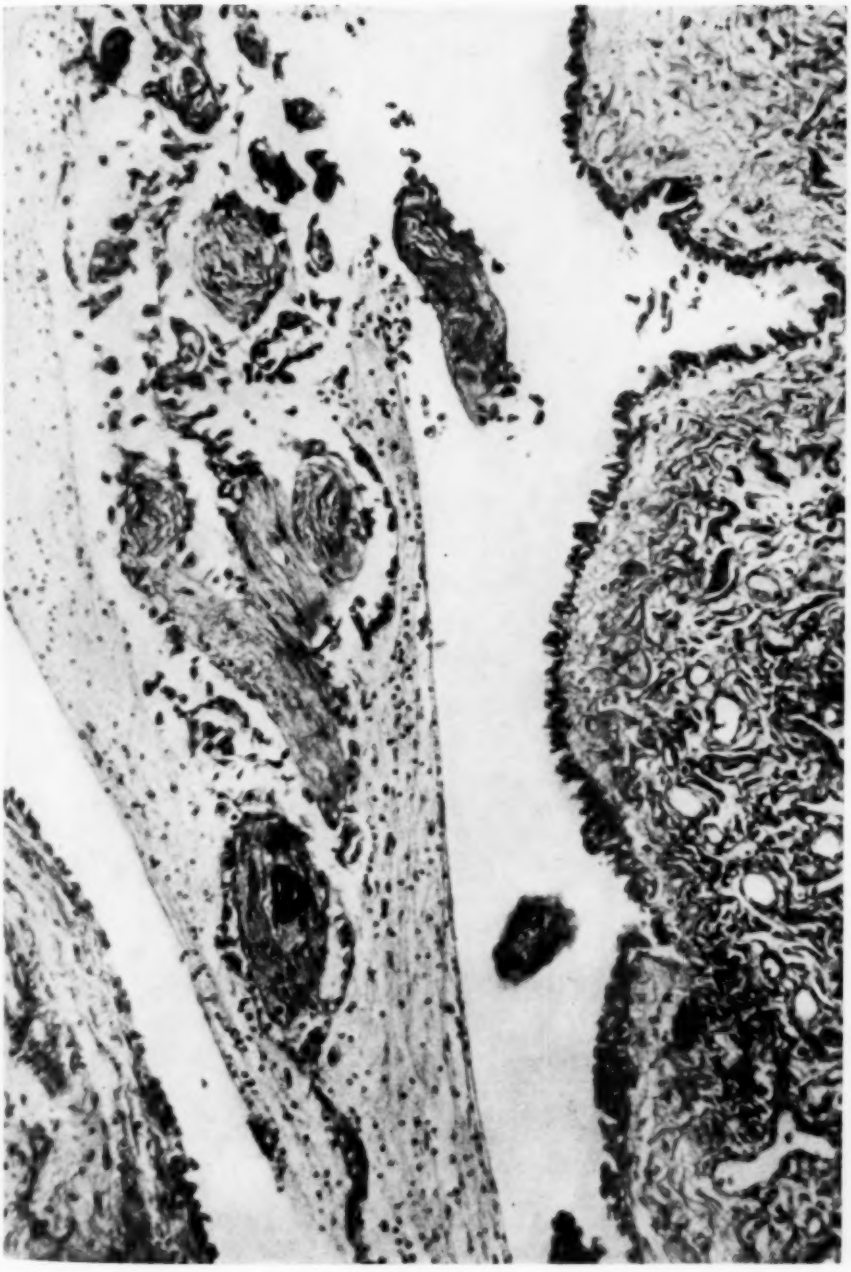

FIG. 1. Low power photomicrograph of visceral pleura with adhesions. Note prominence of mesothelium and deposits of fibrin and leukocytes about adhesions. ×145. (Courtesy of the Army Medical Museum.)

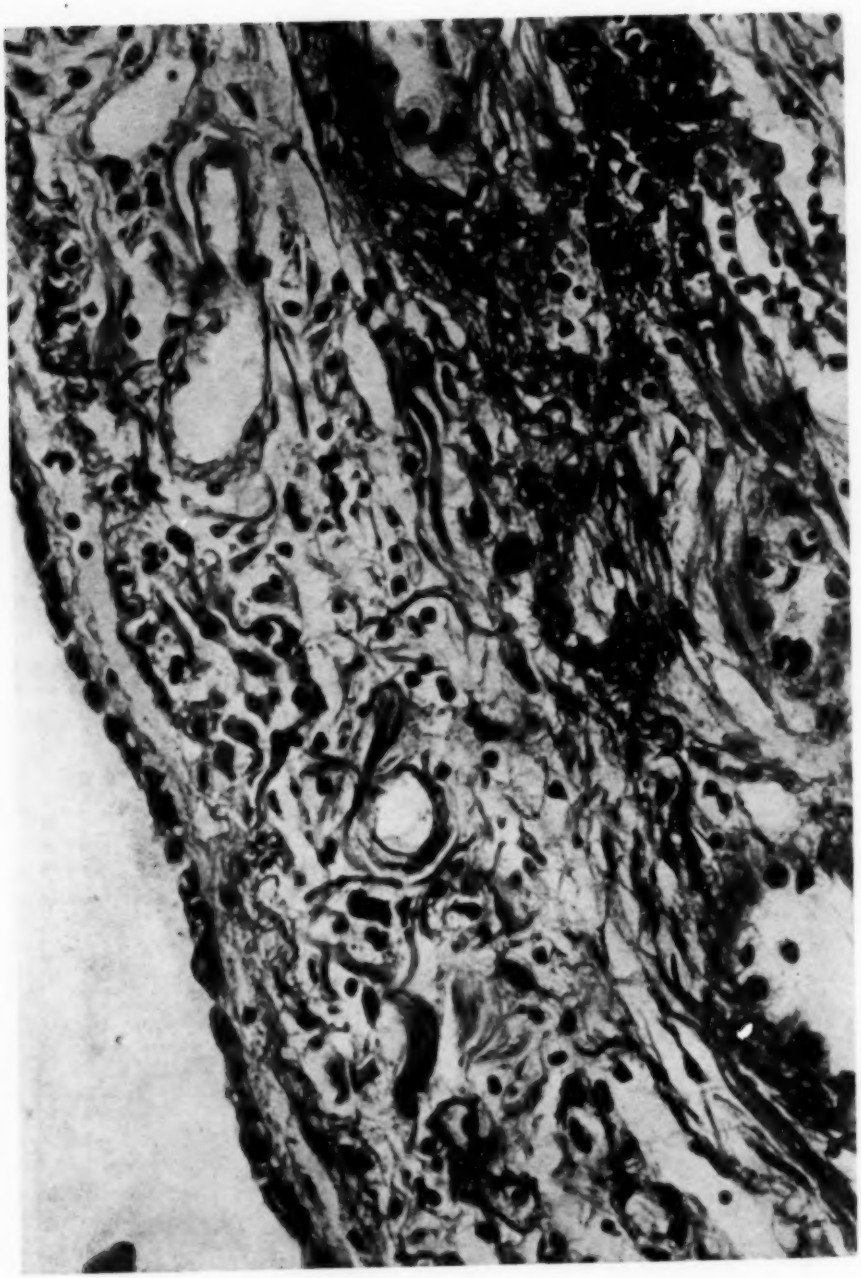

FIG. 2. High power photomicrograph of visceral pleura abutting upon adhesion, showing mesothelial swelling, pleural thickening, increased vascularity, fibrin deposits and leukocytic infiltration. × 500. (Courtesy of the Army Medical Museum.)

FIG. 2. High power photomicrograph of visceral pleura showing [illegible] thickening, increased vascularity, fibrin deposits and leukocytic infiltration. × 500. (Courtesy of the Army Medical Museum.)

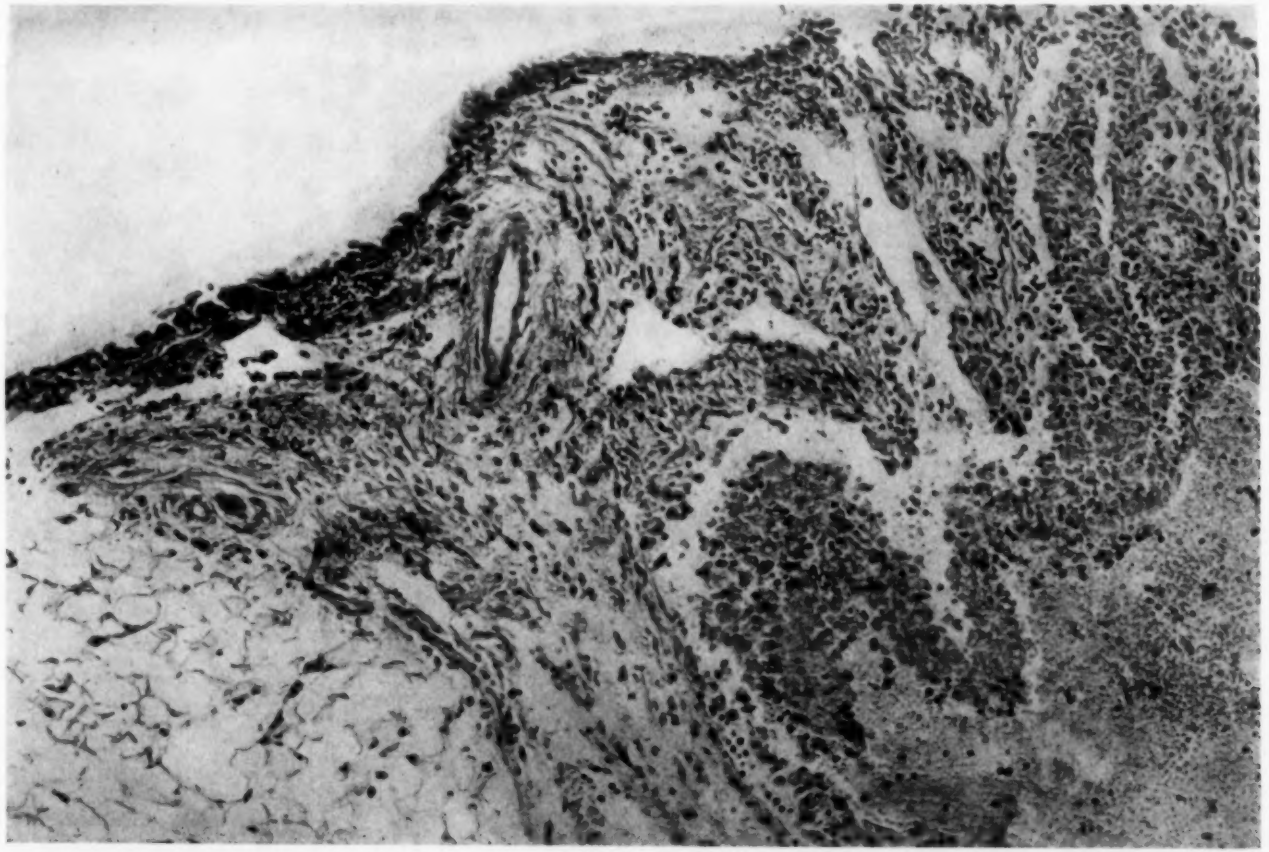

FIG. 3. Low power photomicrograph of parietal pleura showing mesothelial proliferation and marked cellular infiltration with edema near the base of adhesion, along with free blood, fibrin and leukocytes in the pleural space. × 145. (Courtesy of the Army Medical Museum.)

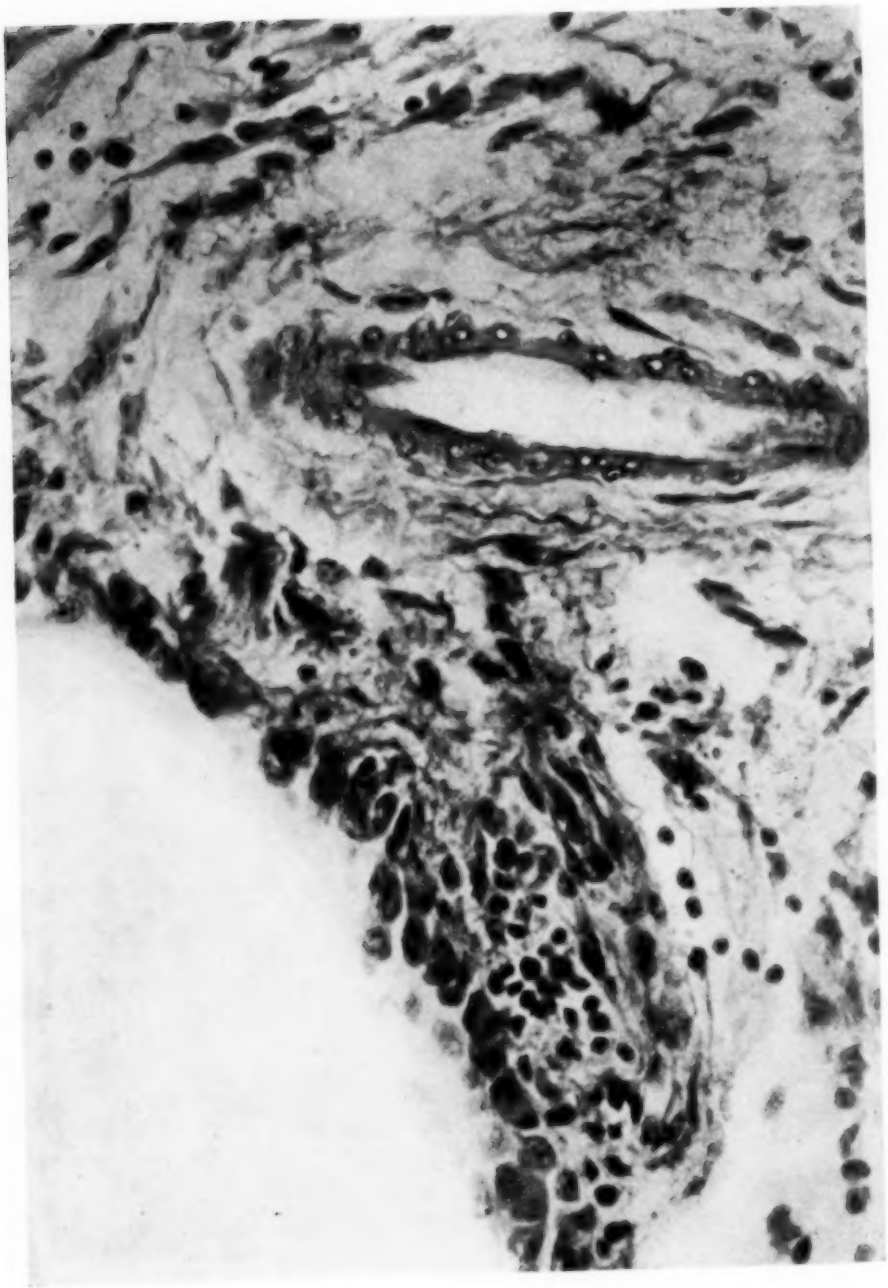

FIG. 4. High power photomicrograph of parietal pleura and adhesion showing mesothelial swelling and proliferation, edema, and leukocytic infiltration with well formed blood vessel. × 500. (Courtesy of the Army Medical Museum.)

was greatly improved and he seemed to be making a satisfactory recovery from his shock until about 6 p.m., when he suddenly again became very restless and breathless. He rapidly went into profound shock and died 15 minutes later.

Autopsy. At the necropsy about 2000 c.c. of fluid blood were found in the left thoracic cavity and the mediastinum was pushed to the right of the midline approximately three inches. The left lung was completely collapsed but was adherent to the left apex by dense adhesions. Three thick cord-like bands from 2 to 4 mm. in diameter were found firmly adherent to the parietal pleura and there were several tough adhesive tags present over the lateral and posterior aspects of the left pulmonary apex. When the adhesive bands between the parietal pleura and apex were severed, it was observed that some small interstitial hemorrhages were present in the adhesions and in the thickened fibrous pleura immediately surrounding these bands. A careful examination of the vascular supply of the lung showed nothing abnormal. There was one small subpleural calcified nodule in the left apex about 3 mm. in diameter. Careful search revealed no evidence of active tuberculosis. The right lung was entirely negative, and the remaining viscera showed no lesions except for a Chiari network in the right cardiac auricle and a mild degree of atheromatous change in the coronary arteries.

Histopathology. Microscopic examination of the viscera showed nothing of importance with the exception of the findings in the left lung and its apical adhesions. The left lung showed thickening of the pleura over most of the upper lobe with prominence of the mesothelial layer, and the underlying alveoli contained many phagocytes laden with brown pigment.

Sections through the visceral pleura abutting upon the adhesions revealed marked prominence and some desquamation of swollen serosal mesothelial cells. Considerable fibrin and white cells were found about the adhesions (figure 1). Higher magnification brought out the pleural thickening and the mesothelial swelling quite strikingly; and also the presence of a moderate infiltration of leukocytes along with some fibrin in the subserosal stroma (figure 2).

Various sections taken through the parietal pleura and the attached adhesive bands again showed the same swollen layer of surface mesothelial cells near the attachment of the adhesions and on the surface thereof. In the adhesions, leukocytes, red cells, fibrin and edema were observed in the subendothelial stroma (figure 3). Under higher power the parietal pleura with its adhesions again showed swelling and proliferation of the mesothelium. Moreover, a well developed vascularity was encountered in many sections of the adhesions, both parietal and visceral (figure 4).

FIG. 4. High power photomicrograph of parietal pleura and adhesion showing mesothelial swelling and proliferation, edema, and leukocytic infiltration with well formed blood vessel. × 500. (Courtesy of the Army Medical Museum.)

DISCUSSION

An examination of the important features of the foregoing case and a study of similar reports in the literature would suggest that the deceased, five days previous to his admission to the hospital, might have torn the well vascularized left, apical, pleural adhesions following the exertion of throwing a heavy bag over his left shoulder. This rupture possibly produced slow bleeding into the left thorax. The patient's symptoms also suggest that the pneumothorax occurred at 2 a.m. on the morning of his hospital admission. It is also hypothesized that the collapse of the left lung might have increased the bleeding from the ruptured adhesions which produced the picture of rapidly developing hemopneumothorax and shock.

In a review of the literature, we found 13 cases of spontaneous hemopneumothorax which came to necropsy and the important clinical and autopsy findings are summarized in the following chart (chart 1).

CHART I

Name and Date	Sex and Age	Nationality and Occupation	Outstanding Clinical Findings	Duration in Days	Side Involved	Past History and Possible Contributory Etiology	Chest X-ray	Aspiration of Blood	Blood Transfusion	Quantity and Character of Blood in Chest	Apical Scars	Bullae	Adhesions	Microscopic Examination	Comments
	Clinical Findings									**Autopsy Findings**					
1. Pitt[3] 1900	♂ 18	Eng. Not given	Gradual development pain right shoulder and chest. First seen in shock.	2	Rt.	5 days previously sore throat and vomiting.	0	+	0	Fluid 4½ L.	0	One apical	1	0	Ruptured adhesion attached to apical bulla.
2. Rolleston[3] 1900	♂ 21	Eng. Not given	Sudden pain right upper quadrant radiating to shoulder. Shock. Diagnosed perf. ulcer.	8	Rt.	None	0	+	0	Fluid 2 L. Few clots	0	0	0	0	No bleeding point found.
3. Fischer[4] 1922	♂ 22	German Cinema techn.	Sharp pain right chest. Wk. later pain right upper quadrant. Shock. Laparotomy for perf. ulcer.	7	Rt.	Cough for one year.	0	+	0	Coagulated 4½ L.	+	Many bilat. apical	0	+	Fresh blood oozed from ruptured bulla.
4. Kaier[4] 1923	♂ 30	Danish Rifleman	Knife-like pain in neck and between shoulder blades. Signs of pneumothorax and fluid.	3	Lt.	Fell from bicycle 2 mo. previous. Struck rib. Severe cold 1 wk.	0	+	0	Not mentioned	0	0	0	0	No lesions lung or pleura.
5. Horsden and Piggott[6] 1931	♂ 44	Eng. Plumber	Severe pain left chest and abdomen. Over period of 4 days developed signs of internal hemorrhage and shock.	4	Lt.	Winter cough for 7 years with pain lt. chest.	0	0	0	Coagulated 1 L.	+	2	2	0	Tough adhesions torn from chest wall.
6. Tait and Wakely[7] 1935	♂ 32	Eng. Sedentary occ.	Pain in chest growing worse over period 4 days with signs of pneumothorax and fluid.	8	Rt.	Lifted end of bed.	0	+	0	Fluid 2½ pts. Not coagulated	0	12 Near apex	0	0	Perforated bulla filled with fresh blood.
7. Rossel[8] 1935	♂ 20	French Soldier	Sudden pain in back with signs of intrapleural hemorrhage and shock.	9	Rt.	Previous roentgen-ray chest negative.	+	+	+	Fluid 3½ L.	0	Several bilat.	0	+	Bilateral pneumothorax. Origin left. Hemothorax not found.

CHART I—*Continued*

	Clinical Findings									Autopsy Findings					
Name and Date	Sex and Age	Nationality and Occupation	Outstanding Clinical Findings	Duration in Days	Side Involved	Past History and Possible Contributory Etiology	Chest X-ray	Aspiration of Blood	Blood Transfusion	Quantity and Character of Blood in Chest	Apical Scars	Bullae	Adhesions	Microscopic Examination	Comments
8. Davidson[9] 1935	♂ 28	Eng. Clerk	On admission signs of intra-pleural fluid with dyspnea and anemia.	21	Rt.	3 wks. prior to admission sudden pain in chest while walking.	0	+	+	Fluid 4 L.	Lt.	0	Lt. apex only	0	No lesion on right except collapsed lung.
9. Davidson[10] 1935	♂ 26	Eng. Tailor	1 day prior to admission sudden pain in right chest with collapse. Admitted in shock.	2	Rt.	None	0	0	0	Fluid 3.2 L.	No	Sev. apical	Both apical	+	Torn adhesions between lung and pericardium. Very vascular.
10. Jones and Gilbert[11] 1936	♂ 23	Amer. Law Student	Knife-like pain lower right chest and upper belly, with signs of pneumothorax and fluid.	38	Rt.	Similar pain to present, 2 wks. and 3 mos. previously.	+	+	+	Fluid blood 4 L. Free fibrin 750 c.c.	Lt.	1	0	+	Bulla not ruptured. Bleeding source not found.
11. Louria[11] 1938	♂ 22	Amer. Barber	Sudden pain in chest with dyspnea. Signs of effusion and anemia.	4	Lt.	Acute intermittent cough.	0	+	+	Not stated	+	1 Lt. Sev. Rt.	+	0	Ruptured apical bulla. Bleeding source not found.
12. Davidson and Simpson[12] 1940	♂ 26	Eng. Soldier	Sudden pain in chest with signs of effusion and rigid belly.	2	Rt.	Following military parade.	0	+	+	2½ L. Fluid and clots	+	1	+	+	Ruptured apical bulla. Vascular torn adhesions at base right.
13. Lorge[13] 1940	♂ 34	Amer. Messenger	Sudden pain in chest followed in few hours by shock.	1	Lt.	Chest pain 2 mos. previously. Fell on back 6 wks. previously.	+	+	0	Fluid 3 L. Few clots	Rt. and Lt.	Few	0	0	Bleeding point not found.
14. Helwig and Schmidt 1945	♂ 30	Amer. Naval Officer	5 days previously sharp pain in chest. 7½ hrs. prior to admission sudden pain followed by shock.	1	Lt.	Slung bag over left shoulder.	+	+	+	Fluid 2 L.	+	0	+	+	3 torn cord-like bands torn from parietal pleura.

Hartzell [1] enumerated 14 cases of spontaneous hemopneumothorax that came to autopsy. A careful examination of his references, however, revealed that the case reported by Perry [14] in 1938 was apparently the same one Davidson [9] had published in 1935. In 1936 Birch [15] discussed a fatal case of spontaneous hemopneumothorax which was complicated by a miniature tuberculous cavity at the apex of the right lung which cavity had not ruptured. Moreover, there was no other evidence of tuberculosis. The right pleural cavity contained several pints of fluid blood and some air. No emphysematous blebs were present and on the anterior aspect of the right upper lobe, an area of roughened pleura was observed, and the escape of air and blood into the chest cavity apparently had its origin here. Neither gross nor microscopic examination, however, revealed any changes of interest. The left lung and remainder of the body were quite normal. This case is given in some detail because it would have been included in the above table had it not been for the minute tuberculous cavity.

An analysis of figure 5 reveals that all of the subjects were males between the ages of 18 and 44. Unusual strain, exertion, or trauma did not seem to be factors in the etiology of the condition and there was nothing significant in the past histories or occupations of the victims. In most instances the first symptoms of acute, sharp, chest pain appeared when the patient was quiet and the onset was not infrequently accompanied by severe, abdominal pain and even rigidity. This latter manifestation was very striking in some cases, so much so in fact that perforated peptic ulcer was diagnosed and, in one instance, an exploratory laparotomy was performed. The duration of symptoms until death ranged from one to 38 days. The right chest was more frequently involved than the left, and the diagnosis of hemothorax was established by aspiration of blood from the affected chest in all but two cases. Removal of air and blood from the thorax and blood transfusions were the only therapeutic measures of importance that were employed.

At necropsy the quantity of blood found in the chest varied from one to four and one-half liters and in most instances the blood was either unclotted or contained only a few clots. In the majority of cases apical pleural scars were observed and in six cases adhesions were found on the involved lung. Emphysematous bullae were observed 10 times, ruptured bullae four times and torn pleural adhesions five times. Microscopic examination of the adhesions in two cases revealed them to be highly vascular. The source of the bleeding was not found in half of the cases. In many instances the origin of pneumothorax was not ascertained, whereas, in three cases, no lesions of the collapsed lung could be discovered.

Conclusions

1. A case of fatal spontaneous hemopneumothorax with necropsy is reported. The intrapleural bleeding appeared to have arisen from torn apical vascular adhesions.

2. An outline of the pertinent facts in the reported fatal cases of the above condition is given and what were considered the significant clinical and pathological data are briefly discussed.

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EDITORIAL

GOLD SALTS FOR RHEUMATOID ARTHRITIS

HAVING returned to many professional and economic changes, the homecoming medical officer will have unfortunately found one condition relatively unchanged; namely, the frustrating problem of rheumatoid arthritis. He will also find still continuing and still unsettled, the prewar controversy over the use of gold salts for rheumatoid arthritis.

Why are the opinions of internists and specialists concerning this treatment so diverse after twenty years of use? Gold salts were first employed for rheumatoid arthritis in Germany about 1927 by physicians who, impressed with results in tuberculosis, regarded rheumatoid arthritis as related to tuberculosis, an unproved untenable notion. First American reports appeared in 1936. During the 15 prewar years thousands of patients who had rheumatoid arthritis were treated and many European and American reports appeared. Most reports strongly favored chrysotherapy but several drawbacks were admitted: not all patients were benefited thereby; many developed relapses; toxic reactions were frequent and occasionally fatal.

Despite the empiric nature of this treatment and the danger inherent therein many physicians of wide experience and mature judgment concluded that gold salts provided "the best single remedy" ever found for this serious disease, and that chrysotherapy deserved further investigation. It was hoped that nontoxic preparations could be developed, that the mode of action of gold salts could be discovered, that more successful schemes of dosage could be evolved, that tests of susceptibility to, or remedies to control, gold intoxication could be devised. To what extent have these hopes been realized since 1942?

Reports of results in more than 2,000 additional American cases and in at least 1,000 foreign cases have appeared.[1, 2, 3, 4, 5] Results varied rather widely: From 6 to 54 per cent of the patients became free of symptoms and more frequently from 10 to 15 per cent obtained "arrests." In an additional 35 to 65 per cent of cases marked improvement was noted. Thus in general about 50 to 60 per cent of patients became symptom-free or were notably relieved.

Of special interest is the three to five year follow-up study of 142

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patients by Ragan and Tyson [6]: 11 per cent were not improved, 76 per cent were improved, and in the remaining 13 per cent complete remissions were obtained; "five year cures" occurred in 6 per cent. Relapses occurred in 75 per cent but 80 per cent of those who relapsed improved under further treatment.

These recent reports are conservative but the results approximate closely those noted between 1927 and 1940. One particular lack has been apparent, the matter of controls. In 1940 Ellman, Lawrence and Thorold [7] obtained remissions in 47 per cent of patients given weekly doses of 200 to 300 mg. of gold salts, in 27 per cent of those given 100 mg. and in only 3 per cent of a control series given injections of sterile almond oil. Recently Fraser,[8] conducting a "blindfold test," noted marked improvement in 42 per cent of patients given gold, in only 8 per cent of patients injected with an inactive control substance prepared to look like the solution of gold. Toxic reactions affected 75 per cent of patients receiving gold, but 37 per cent of the control group experienced rashes, and so forth which had been regarded as "toxic reactions."

Results have been generally better in the earlier stages of the disease.[1, 3] But the disease in many late cases has responded favorably and in some early cases has been refractory.

Originally the amounts of gold injected as a single dose were quite great but they were gradually reduced so that until recently the standard maximal individual doses given in the United States and Great Britain were generally 100 mg. of gold salts (about 50 mg. of gold). But after careful observations Smyth and Freyberg [9] concluded that the optimum maximal dose was 50 mg. of gold salts (about 25 mg. of gold). Such doses were as effective as the larger ones but 25 mg. doses of gold salts were considered insufficient except in mild cases among adults or for children. But others [10] using maximal doses of 25 mg. of gold salts recently reported marked improvement in 53 per cent of their cases, complete remissions in none. Hence the merits of the "smaller dose program" have yet to be determined.

No special merit applies to any one of the numerous gold compounds commercially available. For reasons to be noted hereafter some preparations are less toxic, but less effective, than others.

Even though many patients are notably benefited or even completely relieved, a disturbingly high percentage of relapses develop. Often the gold-induced remissions lasted many months or for two years or so, but the

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relapse rate has varied from 12 to 75 per cent depending on the duration of the studies.

If the foregoing summarized the story of chrysotherapy for rheumatoid arthritis there would be almost unanimous approval and widespread use of this remedy but, unhappily, toxic reactions still provide a great drawback. The incidence of toxic reactions recently has varied from as low as 8 per cent [8] to as high as 75 per cent,[8, 11] these differences depending partly on the activity or relative inertness of the gold preparation used and partly on what the various writers considered to be reactions worthy of note. Most writers noted toxic reactions of some sort in about 40 per cent of patients treated. The reactions were generally mild and transient. In about 3 to 11 (average about 5) per cent of cases reactions were serious (exfoliative dermatitis, agranulocytosis, thrombocytopenic purpura, acute enterocolitis, hepatitis) but were nonfatal.

A few reactions proved fatal but fatal reactions are occurring with increasing rarity. Mortality rates from chrysotherapy, as high as 3 per cent in 1935, and prior to 1939 between 0.5 and 0.6 per cent,[11, 12] have recently been between 0.38 and 0.43 per cent.[1, 2, 4, 6] Deaths occurred from acute enterocolitis, cerebral purpuric hemorrhages, thrombocytopenic purpura or aplastic anemia. Agranulocytosis, the cause of several deaths in previous years, is now controllable by penicillin.[13, 14] Several physicians have used chrysotherapy with no fatalities in small series of from 30 to 100 cases but with wider experience they may also note an occasional fatality.

Occasionally toxic reactions appear early during treatment and probably represent hypersensitivity to gold. But most reactions occur later, after a few hundred milligrams of gold salts have been given: such reactions represent metallic protoplasmic poisoning. Thus most toxic reactions have been related to the accumulated total of individual doses.

Many attempts have been made to prevent reactions by using "gold sensitivity tests" (patch tests or preliminary injections at two day intervals of minute doses of gold) or by the administration, during chrysotherapy, of various vitamins, calcium preparations, liver extracts or bile salts. But statistical evidence having indicated their ineffectiveness, practically all American and British workers have agreed that there is no known way of preventing toxicity. One European pioneer in the use of gold salts stands almost alone in his continuing belief that practically all serious toxic reactions can be prevented by a preliminary period of intensive vitamin therapy.[15]

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Once toxic reactions have occurred, until very recently there has been no known rapid control thereof as they usually continued until an appreciable amount of the injected gold was excreted. Treatment was entirely symptomatic. But recent results with the use of BAL (British Anti-Lewisite) lead us to hope that an effective method for controlling at least some of the serious toxic reactions may be at hand. Nine patients who had exfoliative dermatitis of less than two months' duration, one patient who had severe thrombocytopenic purpura and one who had granulocytopenia, responded rapidly to the intramuscular injections of BAL.[16-18] One patient whose dermatitis has been present for three months was not relieved. Although the number of patients so treated is as yet too small to be conclusive these preliminary results are indeed promising. Despite this new approach to the treatment of toxic reactions the best way to minimize them is to spot them, if possible, in their incipiency and stop the injections immediately, but sometimes only temporarily. To this end frequent clinical and laboratory observations are mandatory. Thus impending skin reactions or blood dyscrasias, the two most troublesome toxic manifestations, may be discovered and treated early.

Were the mode of action of gold salts in rheumatoid arthritis known, the variations in results and in toxicity and the cause for relapses might be explained. Gold salts have certain bacteriostatic and chemotherapeutic properties. But since no bacterial cause of rheumatoid arthritis has been found, these observations do not necessarily apply.

More fruitful than bacteriologic studies have been the investigations of Freyberg, Hartung and their colleagues [9, 19, 20, 21, 22] on the metabolism of gold compounds in the human body. Injected gold salts are dispersed via plasma and deposited in various organs and tissues, chiefly liver and kidneys, from whence they are eliminated (by urine and feces) so slowly that weekly injections build up significant concentrations in plasma and tissues. Thus 75 to 85 per cent of the gold serially injected remains in the body. Significant amounts of gold may be still present in plasma for eight to ten months

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[18] RAGAN, C., and BOOTS, R. H.: The treatment of gold dermatitides; use of BAL (2,3-dimercaptopropanol), Jr. Am. Med. Assoc., 1947, cxxxiii, 752–754.

[19] BLOCK, W. D., and KNAPP, E. L.: Metabolism, toxicity and manner of action of gold compounds in the treatment of arthritis. VII. The effect of various gold compounds on the oxygen consumption of rat tissues, Jr. Pharmacol. and Exper. Therap., 1945, lxxxiii, 275–278.

[20] FREYBERG, R. H.: Recent trends in the treatment of rheumatoid arthritis, Ohio State Med. Jr., 1942, xxxviii, 813–820.

[21] FREYBERG, R. H., BLOCK, W. D., and WELLS, G. S.: Gold therapy for rheumatoid arthritis; considerations based upon studies of the metabolism of gold, Clinics, 1942, i, 537–570.

[22] HARTUNG, E. F., COTTER, J., and GANNON, C.: The excretion of gold following the administration of gold sodium thiomalate in rheumatoid arthritis, Jr. Lab. and Clin. Med., 1941, xxvi, 1750–1755.

after the completion of a "course" in which weekly doses are of 100 mg. of gold salts, for three to five months when 50 mg. is used, for about one month when 25 mg. is used. Gold has been detected in urine 30 to 600 days after the last injection has been given.

All gold compounds are not metabolized similarly. Colloidal gold, deposited chiefly in liver and spleen, is generally quickly phagocytosed by reticulo-endothelium; hence, colloidal gold preparations are generally ineffective therapeutically.

Some workers have concluded that the toxic and therapeutic properties of gold salts are probably largely inseparable; the more harmless a preparation is the less effective it may be. Perhaps gold, by altering the metabolism of certain cells, inhibits an enzyme system a disturbance of which is primarily responsible for rheumatoid arthritis.[6, 19] Perhaps the ameliorating effect of gold in rheumatoid arthritis is analogous to, if not basically identical with, that induced by intercurrent jaundice or pregnancy.[23]

Although many European physicians continue to give doses of gold salts many times greater than 50 or even 100 mg.[15] most American physicians have abandoned the former "course method." To reduce the incidence of toxic reactions and of relapses, maximal weekly doses of 50 mg. of gold salts are now generally used and when articular symptoms abate and sedimentation rates approach normal, the doses are not discontinued but small maintenance doses are continued for several months.[6, 20, 24]

Let us now weigh the arguments for and against chrysotherapy. The "balance sheet" shows that currently a patient so treated has about a 10 to 15 per cent chance of obtaining a "complete remission" lasting from several months to an undetermined number of years, about a 50 per cent additional chance of being notably improved, about a 35 per cent chance of obtaining no significant relief. On the other side of the ledger he has a 50 per cent chance of having no toxic reaction, a 45 per cent chance of having a minor or moderate reaction, a 3 to 5 per cent chance of a serious but nonfatal toxic reaction, and about one chance in 250 (0.4 per cent) of developing a fatal reaction (unless the use of BAL lessens these chances).

The protagonists of chrysotherapy admit that gold salts are dangerous and that physicians giving them are (or should be) "in a constant state of alarm." Despite this, chrysotherapy is superior to any other treatment and is the only method which will markedly change the course of the disease in a significant percentage of cases. To call it the best single agent "does not appear to be a sensational statement when one considers how disappointing most other remedies usually are." [24] Rheumatoid arthritis, the great crippler, produces human wastage of much social and economic importance. Always potentially serious, it represents "big game" and cannot be fought

[23] HENCH, P. S.: The advantages of hepatic injury and jaundice in certain conditions, notably the rheumatic diseases, Med. Clin. North America, 1940, xxiv, 1209–1237.

[24] CECIL, R. L.: The problem of dosage in the administration of gold salts for rheumatoid arthritis, Med. Clin. North America, 1946, xxx, 545–552.

with small caliber weapons. When defensive warfare (use of general measures) is obviously failing, the aggressive application of total offensive war (chrysotherapy) is, despite its risks, justified by the vicious nature of rheumatoid arthritis.

The critics [11, 25] of chrysotherapy properly point out that very few (only two?) control studies have been made; most workers have reported only the "early results" tabulated a few months after the last injection; only a few long time results have been reported. Many reports are difficult to evaluate because their authors have "lumped together 'cures' and 'improvements' to make an impressive showing," have failed to state their criteria for judging results and have failed to classify results in relation to the stage and activity of the disease. The tremendous psychic value of chrysotherapy must be taken into account.

Rheumatoid arthritis is potentially reversible as shown by the fact that many patients are only briefly affected, and those chronically affected may be temporarily "cured" by jaundice or pregnancy. This potential reversibility must not be lost sight of. One critical observer [11] has claimed results from "general measures" (the disease "arrested" in 16 per cent, notably affected in 50 per cent more) equal to or better than those from chrysotherapy. The toxicity inherent in chrysotherapy makes it unsuitable for use by average practitioners without special experience. Gold salts are not constantly effective, are not specific, are at best a palliative and have not been proved to be a necessary adjunct to routine measures.

A strong counterargument is that gold may well accomplish in six months or less what nature or general measures may take six years to accomplish. Surgeons and patients do not hesitate to accept the risks of cholecystectomy or hysterectomy to relieve symptoms much more bearable than those of progressive rheumatoid arthritis. Yet the mortality rates of such procedures are as great or several times greater than that of chrysotherapy. In view of all the foregoing the use of gold salts seems entirely justified (1) in cases of progressive rheumatoid arthritis unrelieved by a reasonable but not too long a period of older and safer methods of treatment, (2) when the patient clearly understands and accepts the risk and (3) when the physician is in a position to give the treatments with the necessary clinical and laboratory safeguards.

Two recent incidents impressed the writer. A visiting physician said "I wish I could use gold but if I did and something happened I'd be run out of town." On another occasion the writer seeing a farmer's wife with progressive rheumatoid arthritis unrelieved by much therapy, told her frankly of the merits and risks of gold injections. The husband spoke up: "You won't give that to my wife and run the risk of killing her. She can't do much but I need her on the farm anyhow." The wife was silent for a minute. Then tears appeared on her cheeks. Turning to her husband and

[25] STEINBROCKER, O.: Therapeutic results in rheumatoid arthritis, Jr. Am. Med. Assoc., 1946, cxxxi, 189–193.

laying a hand on his knee she said quietly, "But John, I'm the one who lies awake in pain week after week. I'm the one who takes the risk. I want to try it."

Thus it appears that to such a venture there are four interested parties (in the order of importance): (1) the patient who takes the chief risk; (2) the physician who risks his peace of mind but probably not his "reputation"; (3) the interested bystanders, chiefly the close relatives, and (4) the community which if enlightened wants no arthritic derelicts as economic liabilities and is certainly sympathetic to the conscientious physician even in his failures. The distressed rheumatoid patient cannot be objective; in desperation he will try anything. Such an attitude does not absolve the physician of his responsibility, rather it enhances it and requires that the physician shall have fully acquainted himself with chrysotherapy either by assiduous reading or preferably by an adequate visit to one of the clinics using such treatment. It is certainly desirable and, by the proper explanations, usually possible to obtain the understanding, if not the approval, of the interested bystanders. When the latter is not forthcoming it is still the right of the afflicted patient and his physician coöperatively to assume the responsibility.

PHILIP S. HENCH

REVIEWS

Agnosia, Apraxia, Aphasia. Their Value in Cerebral Localization. 2nd Edition, revised. By J. M. Nielsen, M.D., F.A.C.P., Assisted by J. P. Fitzgibbon, M.D. 292 pages; 24 × 16 cm. Paul B. Hoeber, Inc., New York. Price, $5.00.

This monograph on the most complex aspect of clinical neurology not only presents a well integrated analysis of the subject, but also interprets the data in a manner that gives them dianostic significance. However, the highly technical nature of the subject would make it difficult for anyone who is not a trained neurologist to apply the detailed information made available.

The entire field of agnosia, apraxia and aphasia is covered thoroughly on the basis of selected cases from a vast literature, and the authors' own clinical and pathological material. Without sacrificing any of the dynamic aspects of cerebral cortex function, the authors have been able to correlate the clinical and pathological data so as to give the latter significant value in cerebral localization. The methods used in arriving at conclusions are clearly portrayed; and they are both theoretically sound and clinically applicable.

A concise and lucid summary is provided in the appendix; and the authors' terminology is correlated with older nomenclature wherever possible, thus affording a basis on which earlier literature can be interpreted in the light of their own concepts.

H. A. T.

The Diagnosis and Treatment of Bronchial Asthma. By Leslie N. Gay, Ph.B., M.D., Assistant Professor of Medicine of the Johns Hopkins University School of Medicine, Director of the Allergy Clinic of the Johns Hopkins Hospital. Foreword by Warfield T. Longcope, A.B., M.D., Professor of Medicine of the Johns Hopkins University School of Medicine, Physician-in-Chief of the Johns Hopkins Hospital, Baltimore. 334 pages; 24 × 16 cm. Williams and Wilkins, Baltimore, Maryland. Price, $5.00.

The author divides the subject of bronchial asthma into seven chapters presented in the following order: the physiology of normal respiration and the asthmatic state; etiology; pathology; diagnosis; complications and differential diagnosis; psychosomatic paroxysms and, lastly, the treatment of the condition.

The book is clearly printed and well arranged. The diagrams and pictures are excellent and beautifully reproduced. They are a distinct addition to the text.

The subject matter reflects the author's wide experience and sound clinical judgment.

It seems to this reviewer that too much space has been allotted to the discussion of the rather elementary subject of pollens and pollen counts in a book designed to cover in detail the whole subject of asthma. Further, the classification of asthma offered, covering as it does over two full pages and consisting of some 45 subdivisions, seems too involved and may tend to complicate rather than clarify for the physician an already confusing subject.

The sections on pathology, diagnosis and treatment are excellent and the one on psychosomatic factors is particularly worthy of consideration as directing attention toward a much neglected phase of the subject. The part played by sinus infection in the etiology of asthma is well presented. A valuable feature in this monograph is the discussion of the use of radium in eradicating nasopharyngeal lymphoid tissue infection, as suggested by Crowe and, applied therapeutically by his and the author's

clinics. It is revolutionary in the therapy of asthma. No one interested in asthma can afford not to avail himself of this book.

H. M. B.

Office Endocrinology. Third Edition, revised and enlarged. By ROBERT B. GREENBLATT, B.A., M.D., C.M. 303 pages; 23.5 × 15.5 cm. 1947. Charles C. Thomas, Springfield, Ill. Price, $4.75.

This new and revised edition is better arranged than previous ones, is readily readable and well up to date. The two new chapters on the relation between the endocrine, vegetative-nervous and hypothalamico-pituitary systems are too brief to accomplish more than stimulation of interest. The chapter on the mechanism of uterine bleeding is an excellent presentation of this subject in a short space. The entire book is characterized by an absence of extraneous material. The increasing importance of the use of progesterone in endocrine therapy is well brought out. However, only brief mention is made of the gonadotropic hormones. The physician who has some basic knowledge of endocrinology will find this book an interesting and valuable addition to his library. The average practitioner will find recommended methods of therapy too complex and not sufficiently well defined to be of much practical value.

R. E. B.

Skin Disease in Children. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia University, and ANTHONY C. CIPOLLARO, M.D., Associate in Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia University. 448 pages; 24 × 16 cm. 1946. Paul B. Hoeber, Inc., New York and London. Price, $7.50.

This text adequately presents the subject of skin diseases in children. The subject matter is presented in a way to make it of value to the student of dermatology as well as to the practitioner of pediatrics. There are a number of good illustrations of the more common conditions. The first chapter, on the care of the skin, is excellent. In the opinion of the reviewer such a chapter should be included in the larger texts on general dermatology. The authors state that acne vulgaris and leprosy have been included in the chapter on pyogenic conditions for convenience, but it is difficult to understand why, as neither of these conditions is basically related to pyogenic bacteria. Throughout the text the authors stress the importance of diagnosis prior to the institution of therapy. The various diagnostic aids are thoroughly reviewed. The chapter on syphilis in children by Dr. Herman Beerman is excellent. Physicians who treat children will find this monograph a valuable reference.

H. M. R., JR.

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Modern Dermatology and Syphilology. Second Edition. By S. WILLIAM BECKER, M.D., and MAXIMILIAN E. OBERMAYER, M.D. 1017 pages; 26 × 18.5 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, $18.00.

The Treatment of Diabetes Mellitus. Eighth Edition, revised. By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., HOWARD F. ROOT, M.D., PRISCILLA WHITE, M.D., ALEXANDER MARBLE, A.M., M.D., and C. CABELL BAILEY, M.D. 861 pages; 24 × 15 cm. 1947. Lea & Febiger, Philadelphia. Price, $10.00.

The Chemical Kinetics of the Bacterial Cell. By C. N. HINSHELWOOD, R.R.S. 284 pages; 24.5 × 16 cm. 1947. Oxford University Press, New York. Price, $6.75.

Tratado de Patologia Digestiva. By C. BONORINO UDAONDO and M. R. CASTEX. 1297 pages; 26.5 × 17 cm. 1946. Lopez & Etchegoyen, S.R.L., Buenos Aires.

Tumores y Seudotumores de la Mama. By JACINTO MORENO, M.D. 142 pages; 23 × 16 cm. 1946. Lopez & Etchegoyen, S.R.L., Beunos Aires.

Office Endocrinology. Third Edition, revised and enlarged. By ROBERT B. GREENBLATT, B.A., M.D., C.M. 303 pages; 23.5 × 15.5 cm. 1947. Charles C. Thomas, Springfield, Ill. Price, $4.75.

Practical Physiological Chemistry. Twelfth Edition. By PHILIP B. HAWK, Ph.D., BERNARD L. OSER, Ph.D., and WILLIAM H. SUMMERSON, Ph.D. 1323 pages; 23.5 × 16 cm. 1947. The Blakiston Company, Philadelphia. Price, $10.00.

The Preservation of Proteins by Drying. Special Report Series. By R. I. N. GREAVES. 54 pages; 24.5 × 15 cm. 1946. His Majesty's Stationery Office, London. Price, 60 cents.

The Cultivation of Viruses and Rickettsiae in the Chick Embryo. Special Report Series. By W. I. B. BEVERIDGE and F. M. BURNET. 92 pages; 24.5 × 15 cm. 1946. His Majesty's Stationery Office, London. Price, 60 cents.

COLLEGE NEWS NOTES

New Life Members

The College is gratified to announce the following additional Life Members, listed in the order of subscription:

Robert S. Dow, M.D., F.A.C.P., Portland, Ore.
Arthur Lee Osterman, M.D., F.A.C.P., Wheeling, W. Va.
Everett E. Hammonds, M.D., F.A.C.P., Birmingham, Mich.
Henry Clay Long, M.D., F.A.C.P., Knoxville, Tenn.
Delbert H. McNamara, M.D., F.A.C.P., Santa Barbara, Calif.
Aldis A. Johnson, M.D., F.A.C.P., Council Bluffs, Iowa
George O. Solem, M.D., F.A.C.P., Chicago, Ill.
Edward C. Koenig, M.D., F.A.C.P., Buffalo, N. Y.
James Steele, M.D., F.A.C.P., Brooklyn, N. Y.
James R. Gudger, M.D., F.A.C.P., New York, N. Y.
John Noll, Jr., M.D., F.A.C.P., Youngstown, Ohio
Henry Allen Tadgell, M.D., F.A.C.P., Belchertown, Mass.
Harry L. Huber, M.D., F.A.C.P., Chicago, Ill.
George F. Lull, M.D., F.A.C.P., Chicago, Ill.
Robert Henry Southcombe, M.D., F.A.C.P., Spokane, Wash.

The Thirteenth Annual Meeting of the American College of Chest Physicians will be held at Atlantic City, N. J., June 5–8. An interesting scientific program has been planned. Oral and written examinations for Fellowship will be held on June 5.

The American Academy of Allergy and the Medical Faculty of the University of California will offer an Orientation Course in Clinical Allergy for General Practitioners, at the University of California Hospital, San Francisco, July 7–11, 1947. Detailed information concerning this course may be had by writing to Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, Calif.

The Fourth Annual Meeting of the American Society for Research in Psychosomatic Problems will take place May 3 and 4, 1947, at Haddon Hall, Atlantic City, N. J. Details of program and arrangements may be secured from the Society's office, 714 Madison Ave., New York 21, N. Y.

The Royal College of Physicians and Surgeons of Canada has announced the following schedule of examinations for the fall of 1947. Applications for these examinations must be in the hands of John E. Plunkett, M.D., F.R.C.P.(C), Honorary Secretary, 150 Metcalfe Street, Ottawa, Can., before June 30.

Written examinations for Fellowship will be held October 27, 28 and 29. Oral and clinical examinations for Fellowship will be held November 24, 25, 26 and 27. Written examinations for Certification will take place October 27 and 28; oral and clinical examinations, November 17 and 18.

Written examinations will be given at Vancouver, Edmonton, Saskatoon, Winnipeg, London, Toronto, Kingstone, Montreal, Quebec City and Halifax. Oral and

clinical examinations will be given at Toronto only. For further information, regulations and application forms, address Dr. Plunkett.

AMERICAN COLLEGE OF PHYSICIANS RESEARCH FELLOWS IN MEDICINE, 1947–48

The Committee on Fellowships and Awards of the College, acting under authorization granted by the Board of Regents, has awarded five additional Research Fellowships in Medicine for the year which begins July 1, 1947. The earlier appointment to a Fellowship for this period of Dr. Tom Fite Paine, Jr., Aberdeen, Miss., was announced last December. Notifications of appointment have been sent to the following physicians.

WARD S. FOWLER, M.D., Philadelphia, Pa. Dr. Fowler will conduct studies of the pathological physiology of certain primary disorders, under the supervision of Dr. Julius H. Comroe, Jr., F.A.C.P., at the Graduate School of Medicine of the University of Pennsylvania. Dr. Fowler is a graduate of Swarthmore College (1937) and of the Harvard Medical School (1941). Dr. Fowler interned at the Philadelphia General Hospital, 1941–42, and served as a medical officer in the U. S. Army Air Forces.

ARNOLD LIVINGSTONE JOHNSON, M.D., C.M., Montreal, Can. Dr. Johnson will continue his investigation of the hemodynamics of congenital heart disease in the Children's Memorial Hospital and the Department of Physiology, McGill University, under the direction of Dr. Alton Goldbloom and Professor H. E. Hoff. Dr. Johnson received the B.A. degree from McGill University in 1935, and his medical degree in 1940. His internship was taken at the Montreal General Hospital in 1941. Dr. Johnson subsequently served as medical officer in the Royal Canadian Navy Medical Corps.

MARY ANN PAYNE, M.D., New York, N. Y. Dr. Payne will undertake at the New York Hospital, where she presently holds appointment as Assistant Resident in Medicine, studies of hepato-renal factors in regard to shock and hypertension. Her supervisors will be Dr. David P. Barr, F.A.C.P., and Dr. Ephraim Shorr. Dr. Payne is a native of Braddock Heights, Md. Her undergraduate work was done at Hood College; she received the degrees of Master of Science (1941) and Doctor of Philosophy (1943) from the University of Wisconsin. Dr. Payne completed her medical course at the Cornell University Medical College in 1945, following which she served as intern in the New York Hospital.

MIRIAM MELLON PENNOYER, M.D., St. Louis, Mo. Dr. Pennoyer, a former resident of Pittsburgh, Pa., received the B.S. degree from Carnegie Institute of Technology in 1935. Her M.D. degree was received from the University of Rochester in 1939. From 1939 to 1944, Dr. Pennoyer engaged in postgraduate work in pediatrics in the University of Minnesota Hospitals.

Dr. Pennoyer will investigate adrenal function in newborn and premature infants at the St. Louis Children's Hospital, under the direction of Professor A. F. Hartmann of the Washington University School of Medicine.

PHILIP FRANKLIN WAGLEY, M.D., Baltimore, Md. Dr. Wagley proposes to study certain mechanisms of hemolysis. These studies will be conducted at the Boston City Hospital, with the supervision of Dr. William B. Castle, F.A.C.P., and Dr. George R. Minot, F.A.C.P.

Dr. Wagley is a native of Mineral Wells, Tex. His undergraduate work was taken at Southern Methodist University, and his medical course at the Johns Hopkins University Medical School, from which he received the M.D. degree in 1943. From 1943 to 1945, Dr. Wagley was intern in pathology and in medicine in the Johns Hopkins Hospital; since 1945 he has held appointment as Instructor in Medicine and Assistant Resident Physician.

President David P. Barr has appointed Walter Freeman, M.D., F.A.C.P., as representative of the American College of Physicians in the Division of Medical Sciences of the National Research Council for a term of three years, beginning July 1, 1947. As College representative, Dr. Freeman will succeed Wallace M. Yater, M.D., F.A.C.P., Governor for the District of Columbia.

Regional Meetings of the College

Richmond, Virginia, February 19

A very successful Regional Meeting of the College for Fellows and Associates in Virginia was held at the McGuire General Hospital, Richmond, February 19, under the Governorship of Dr. J. Edwin Wood, Jr., Charlottesville.

Dr. Charles M. Caravati, F.A.C.P., Richmond, chairman of the Virginia group, presided at the afternoon session, at which there were about 200 physicians present. The program of this session included some very interesting papers, a number of which were presented by young physicians, some of whom were Associates of The College. The speakers were then brought to the stage together to form a panel of consultants before whom were brought patients illustrating the papers which had been presented.

Speakers following the dinner at the Richmond Academy of Medicine included Dr. Wood; Dr. Edward L. Bortz, Governor for Eastern Pennsylvania; Mr. E. R. Loveland, Executive Secretary of The College; Dr. Walter B. Martin, Regent, Norfolk; Dr. Paul F. Whitaker, Governor for North Carolina, Kinston; Dr. William B. Porter, Richmond, new representative of The College on the American Board of Internal Medicine. Dr. Porter spoke at some length concerning the Board's methods of conducting examinations, and of its plans for improving the written examinations.

Omaha, Nebraska, March 29

With College Governor Joseph D. McCarthy, M.D., F.A.C.P., as chairman, a Regional Meeting for Nebraska was held at the Omaha Athletic Club on Saturday, March 29. The program of guest speakers at the dinner included Harold C. Lueth, M.D., F.A.C.P., Dean and Professor of Internal Medicine, University of Nebraska College of Medicine, whose topic was "The Internist and the Hospital"; Charles M. Wilhelmj, M.D., Dean and Professor of Physiology, Creighton University School of Medicine, "Neuropsychiatry as a Fundamental in the Treatment of the Internist"; Ralph A. Kinsella, M.D., F.A.C.P., College Governor for Missouri, Professor of Internal Medicine, St. Louis University School of Medicine, who discussed "Trends and Their Effect on Physicians and the Practice of Medicine."

The following scientific papers were presented at the afternoon session: Recent Studies on the Recording of Heart Sounds, by F. Lowell Dunn, M.D., F.A.C.P.; Amebiasis—The Possibility of Missing Correct Diagnosis Because of Related Findings, by Ernest L. MacQuiddy, M.D., F.A.C.P.; Bulbar Poliomyelitis, Epidemiology and Treatment, by J. Harry Murphy, M.D. (Associate); Treatment of Cirrhosis of the Liver, by Ben Slutzky, M.D., F.A.C.P.; Chronic Encephalitis—Irregularities in History: Obscure Physical Findings, by Harrison A. Wigton, M.D., F.A.C.P.; Dermatologic Reactions to Drugs and Antibiotics, by Donald J. Wilson, M.D., F.A.C.P.; all of Omaha; Congestive Heart Failure, by Otto A. Kostal, M.D. (Associate), Hastings; The Choice and Use of Insulin, by Floyd L. Rogers, M.D., F.A.C.P., Lincoln.

Salt Lake City, Utah, March 29

With Governor Louis E. Viko, F.A.C.P., as director, a Regional Meeting for the College in Utah was held at Salt Lake City on Saturday, March 29. Fellows and Associates residing in Idaho were also invited to participate. At the time of this writing, the program was not available but will be printed in a later issue.

The American College of Physicians delivered a check in the amount of $1,000.00 during January as a donation to the work of The American Heart Association in connection with the Committee on the Study, Prevention and Cure of Rheumatic Fever, a nation-wide project now under way. The title of the Committee has now been officially changed to the American Council on Rheumatic Fever of the American Heart Association, and the member organizations include the American Academy of Pediatrics, American Association of Medical Social Workers, American Heart Association, American Hospital Association, American Medical Association, American Nurses Association, American Public Health Association, American Rheumatism Association, American School Health Association, National Organization for Public Health Nursing, National Society for Crippled Children and Adults and The American College of Physicians.

The Council recently distributed 100,000 copies of its published pamphlet, "Rheumatic Fever, Childhood's Greatest Enemy."

Arie C. van Ravenswaay, M.D., F.A.C.P., Boonville, Mo., is a recipient of the Legion of Merit. The award was made in recognition of Dr. van Ravenswaay's achievements with respect to preservation of health of personnel of the Army Air Forces during his service in the Army of the United States.

The Legion of Merit has been conferred upon Dr. William P. Corr, F.A.C.P., Riverside, Calif., who retired from the Army of the United States in January, 1946, with the rank of Colonel. The distinction was won by Dr. Corr's exceptional services as Chief of the Professional Services of Dibble General Hospital, Menlo Park, Calif., October, 1943, to June, 1945. "He displayed at all times a wide knowledge of all phases of internal medicine, quiet yet forceful leadership and high ideals of the practice of medicine."

The Legion of Merit has been awarded to Colonel John C. Woodland, (MC), USA, Ret'd., F.A.C.P., San Antonio, Tex., for "exceptionally meritorious services" while Chief of Medical Service and Commanding Officer, Brooke General Hospital, December, 1941 to March, 1946. Reference is made to important discoveries which were made concerning virus and rickettsial diseases in studies carried out under Colonel Woodland's supervision.

Thomas H. Ham, M.D., F.A.C.P., Boston, Mass., who retired from the Army of the United States in May, 1946, with rank of Lieutenant Colonel, is a recipient of the Legion of Merit. The award recognizes Dr. Ham's distinguished accomplishments as a member of the Medical Division, Office of the Chief of Chemical Warfare Service, September, 1943, to January, 1946.

Dr. Richard H. Lyons, F.A.C.P., Ann Arbor, Mich., Associate Professor of Medicine in the University of Michigan School of Medicine, has been appointed

Edward C. Reifenstein Professor of Medicine in the Syracuse University School of Medicine. Dr. Lyons will begin his new work in June, 1947.

Dr. Hugh S. Cumming, F.A.C.P., Washington, D. C., formerly Surgeon General of the U. S. Public Health Service, has been elected Director Emeritus of the Pan American Sanitary Bureau, of which he served as Director for twenty-six years. Dr. Cumming has been succeeded in the latter position by Dr. Fred L. Soper, of the Rockefeller Foundation.

Dr. Walter A. Bloedorn, F.A.C.P., Washington, D. C., Dean of the George Washington University School of Medicine, has been elected to the position of President-elect of the Society of American Medical Colleges.

Dr. Albert E. Russell, F.A.C.P., presently attached to the American Consulate General, Naples, Italy, has been promoted to the permanent grade of Medical Director (Colonel) in the U. S. Public Health Service.

The honorary degree of Doctor of Laws was recently conferred on Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, by Columbia University.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to March 13, 1947 inclusive).

Philip K. Arzt, St. Paul, Minn. (Capt., MC, AUS)
John T. Bennett, Philadelphia, Pa. (Capt., MC, USN)
William W. Davies, Coral Gables, Fla. (Capt., MC, USN)
Sidney L. Penner, Stratford, Conn. (Capt., MC, AUS)
Arthur J. Revell, Pittsburg, Kans. (Lt. Col., MC, AUS)
David L. Robeson, Kansas City, Mo. (Col., MC, USA)
Rafael Rodriguez-Molina, Santurce, P. R. (Lt. Col., MC, USA)
Raymond E. Scott, San Antonio, Tex. (Col., MC, AUS)

OBITUARIES

DR. JOHN FAVILL

Dr. John Favill was born in Madison, Wis., September 6, 1886, the son of Henry Baird Favill, distinguished Chicago internist. He died at his home in Winnetka, Ill., December 21, 1946, of coronary thrombosis. He is survived by his widow, Alice Morrell Favill, and a daughter, Elaine, age 10.

Dr. Favill received his A.B. degree from Yale University in 1909; his M.D. degree from Harvard Medical School in 1913. He interned at the Massachusetts General Hospital.

An excellent teacher, Dr. Favill rose to the position of Clinical Professor of Neurology (Rush) in the University of Illinois College of Medicine. He was a diplomate of the American Board of Psychiatry and Neurology. During his career he was affiliated with St. Luke's, Presbyterian, St. Elizabeth's and Cook County Hospitals; also with the Central Free Dispensary and the Institute for Psychoanalysis.

Dr. Favill served as Captain in the Army Expeditionary Force in 1918–19, and as Colonel (inactive status) in the Army Medical Reserve Corps from 1931 on.

He was a Trustee of the Elizabeth McCormick Memorial Foundation. He was a fellow or member of the American Medical Association, American Neurological Association, American Psychiatric Association, Association for Research in Nervous and Mental Diseases, American Society for Psychical Research, Association for the Study of Internal Secretions, Association of Military Surgeons; of the American Birth Control League, National Committee on Planned Parenthood, National Committee for Mental Hygiene, National Dairy Association, American Unitarian Association; of the Institute of Medicine of Chicago and of many state and local medical societies, in a number of which he held offices.

Dr. Favill was the author of more than thirty monographs and papers on medical subjects, and of the following books: "Henry Baird Favill, Life Tribute and Writings," 1917; "Outline of the Cranial Nerves," 1933; "The Relation of Eye Muscles to Semicircular Canal Currents in Rotationally Induced Nystagmus," 1936; "Primer of Celestial Navigation," 1940; "Outline of Spinal Nerves," 1946.

Dr. Favill was scrupulously fair in all of his dealings with others and clung tenaciously to his convictions, regardless of consequences.

GEORGE H. COLEMAN, M.D., F.A.C.P.

DR. A. LEE BRISKMAN

Dr. A. Lee Briskman was born September 29, 1902, in Louisville, Kentucky, where he lived until 1927 when he took his internship at the

Gorgas Hospital, Canal Zone. Prior to this Dr. Briskman had obtained his B.S. and M.D. degrees from the University of Louisville. Following completion of his internship Dr. Briskman served the Union Printer's Home and Tuberculosis Sanatorium as a resident physician between the dates of 1929 and 1944. During this time he was also instructor in pathology at the Glockner Sanatorium and Hospital.

In 1944 Dr. Briskman moved to Denver as Medical Director of the Jewish Consumptives Relief Society. At the time of his death Dr. Briskman had just resigned from this position with the expectation of entering private practice in Denver.

Dr. Briskman became a Fellow of the American College of Physicians in 1934. He was certified by the American Board of Internal Medicine and was a Fellow of the American Medical Association. He was President of the Colorado Tuberculosis Association. He died suddenly November 26, 1946, while speaking in Colorado Springs in the interests of this organization.

WARD DARLEY, M.D., F.A.C.P.,
Governor for Colorado

DR. JAMES STEWART GAUMER

Dr. James Stewart Gaumer, F.A.C.P., died at Fairfield, Iowa, on September 10, 1946, at the age of 74 years. He was one of the older Fellows of the College, having been elected in 1920.

Dr. Gaumer was born in Victor, Iowa, September 13, 1872, and received his Bachelor of Science degree at Parsons College, after which he entered Rush Medical College in Chicago, graduating with the degree Doctor of Medicine in 1900. He began practice in Danville, Iowa, and moved to Fairfield in 1906, where he continued to practice until the time of his death. His practice was largely limited to internal medicine. He was affiliated with the County and State Medical Societies, and a member of the American Medical Association. For many years he was one of the instructors in the Nurses Training School of Jefferson County Hospital. His military experience began with the Spanish American War when he served as a Sergeant, Company M, 50th Iowa Volunteers; in the World War I he was a Lieutenant in the Medical Corps of the A.U.S.

He is survived by his wife, one son and one grandson.

He was an ethical physician and a high minded citizen.

WALTER L. BIERRING, M.D., F.A.C.P.

DR. R. H. M. HARDISTY

The death of Dr. Richard Hardisty in Montreal, Nov. 12, 1946, of coronary thrombosis at the age of 69, brought a great sense of loss to his col-

leagues, friends and patients, as well as to the two institutions which he had served so faithfully and with such distinguished ability, McGill University and the Royal Victoria Hospital.

Graduating from McGill University in Arts and Medicine, Dr. Hardisty served a three year internship at the Royal Victoria Hospital, followed by four years in general practice at Sherbrooke, P. Q., and by a year's post-graduate study in Munich, Berlin, Vienna and London. Dr. Hardisty returned in 1910 to Montreal to practise Internal Medicine with special interest in Gastro-Enterology. He joined the staff of the Medical School in 1930 as Lecturer in Medicine, and the Royal Victoria Hospital as Physician in 1935. He retired to the honorary attending staff in 1943. To both of these institutions he gave untiringly of his outstanding ability as teacher and clinician.

In World War I, Dr. Hardisty served in the Field for over four years with the 6th Canadian Field Ambulance, which he helped to organize, and of which he later became Commanding Officer with the rank of Lt. Colonel. During these years of military service, he was awarded the Distinguished Service Order, the Military Cross, and was twice mentioned in Dispatches, honors which were well merited and worn with all modesty.

He was a member of the Canadian Medical Association, the American Gastro-Enterological Association and Fellow of The American College of Physicians since 1929.

Of his personal side much could be said. Through his unfailing kindness and consideration for others, his rare sense of humor, his unswerving loyalty and his genuineness, he bore the hall mark of the true gentleman and the beloved physician. We in Montreal who knew him well are the poorer for his going, but all the richer for having known him.

He is survived by his widow, the former Elizabeth Porter of Montreal, and by a brother, Alfred.

ARTHUR T. HENDERSON, M.D., F.A.C.P.,
Governor for Quebec

DR. LUCIUS NEWTON TODD

Lucius Newton Todd, M.D., F.A.C.P., Augusta, Ga., died after a prolonged illness on December 12, 1946.

Dr. Todd was born in Belton, S. C., October 9, 1890. Following three years of premedical study at Emory University, he attended the University of Georgia School of Medicine and received the M.D. degree in 1915. He interned at the University Hospital, 1915–16. Soon after opening an office in Greenville, S. C., he developed pulmonary tuberculosis. To combat the early rapid progress of this disease required a stamina which few possess and, from 1916 to 1923, Dr. Todd stoically fought an uphill battle at several centers for the treatment of tuberculosis, Saranac Lake, Asheville, and

Colorado Springs. He resumed his medical activities as Resident Physician at Cragmor Sanatorium, 1923–24, and at Sunmount Sanatorium in New Mexico, 1924–25. He served at the U. S. Public Health Service Hospital No. 9 in New Mexico, 1925–28, and was senior resident at the Waverly Hill Sanatorium in Kentucky, 1928–37. In 1937 he was appointed the first Professor of Tuberculosis at the University of Georgia School of Medicine, and Chief of the Tuberculosis Service in the University Hospital. He also acted as Tuberculosis Clinician for the Aiken, S. C., Hospital and Relief Society. Dr. Todd was a Fellow of the American Medical Association; a member of the American Trudeau Society, American College of Chest Physicians, and of the Southern Sanatorium Association (Secretary, 1937–38). He became a Fellow of the American College of Physicians in April, 1944.

As a teacher Dr. Todd possessed the ability to transmit his knowledge and experience to his students. His outstanding success in establishing a Tuberculosis Center was evidenced by his election to honorary membership in the Alpha Omega Alpha Fraternity in 1945. As a physician, his personal experience provided him with a keen understanding of the problems of his patients, and his kindliness and encouragement carried the weight of a fellow-sufferer. The Department of Tuberculosis at the University of Georgia School of Medicine will remain as a memorial to its first director and organizer, Dr. Lucius N. Todd.

EDGAR R. PUND, M.D., F.A.C.P.

DR. ROBERT VAN VALZAH

Robert Van Valzah, M.D., F.A.C.P., was born in Spring Mills, Pa., November 1, 1882. His early education was obtained at Bellefonte Academy, and in 1904 he received an A.B. degree from Princeton University. Upon his graduation from the University of Pennsylvania School of Medicine in 1908, where he was elected to Alpha Omega Alpha, he became the third physician in direct line in his family. This tradition had continued for five generations in this country with but one interruption. In 1908 he served an internship at St. Christopher's Hospital for Children, Philadelphia, after which he became Chief Resident at the Hospital of the University of Pennsylvania in that city.

He joined the Department of Internal Medicine in the University of Wisconsin in 1910, as an instructor, advancing to the position of Professor of Clinical Medicine in 1918. This position he held until his death, November 23, 1946, although, because of ill health, he was granted an official leave of absence in 1935. His position remained open to him with the hope that he would be able to return. In his earlier clinical years he was Director of the Department of Student Health at the University of Wisconsin and later, upon the completion of The State of Wisconsin General

Hospital, he served on its staff. He was a member of the Dane County and the Wisconsin State Medical Societies, and a Diplomate of the American Board of Internal Medicine. During the first World War he was Chairman of the Medical Advisory Board in his district.

To the State of Wisconsin and to the University of Wisconsin Medical School, then in its infancy, Dr. Van Valzah brought an unusual background of medical tradition and training. He was an indefatigable worker, whose life was intimately associated with the student body of the University as physician, and later with the medical students as teacher. His strong character and attractive personality together with a background of excellent medical training did much for the development of the University of Wisconsin Medical School in its pioneering clinical years. At that time he was widely sought as a medical consultant. He was a doctor's doctor, whose memory will be cherished by many people, and whose influence will long be felt by the physicians who trained under him.

KARVER L. PUESTOW, M.D., F.A.C.P.,
Governor for Wisconsin

DR. JOSEPH ROSENFELD

Joseph Rosenfeld, M.D., F.A.C.P., Youngstown, Ohio, died November 4, 1946, of periarteritis nodosa, a diagnosis he had long suspected and which was proved at the postmortem examination which he specifically requested be performed on his body.

Dr. Rosenfeld was born in New York City, November 5, 1892, and received the Degree of Doctor of Medicine in 1915 from the Long Island College Hospital. He served as a Medical Officer with the Mount Sinai Unit of New York during World War I, and received honors from the British, French, and American Armies for meritorious service.

He was for many years Associate in Medicine and Instructor of Medicine to Nurses of the Youngstown Hospital. He was a Fellow of the American Medical Association and a member of the Mahoning County Medical Society, Ohio State Medical Association and Cleveland Allergy Society. He became a Fellow of The American College of Physicians in 1940.

Dr. Rosenfeld was a man of many intellectual interests, a fine gentleman, and a credit to his profession.

M. A. BLANKENHORN, M.D., F.A.C.P.,
Governor for Ohio

DR. PAUL ROTH

Paul Roth, M.D., F.A.C.P., of Battle Creek, Michigan, died November 6, 1946. He was born in Tramelan, Switzerland, July 9, 1871; he received his early elementary education in that country. He attended the Battle

Creek College and received his medical degree from the American Medical Missionary College (Chicago) in 1904. He interned at the Battle Creek Sanitarium and served there in numerous capacities after 1910. He was at one time on the faculty of the Battle Creek College, and Consultant in Oxygen and Carbon Dioxide Therapy at the Kellogg Foundation.

He was a member of the Calhoun County Medical Society, Michigan State Medical Society, American Medical Association, Association for the Study of Endocrinology, the American Chemical Society. He became a Fellow of the College in 1920.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. ROBERT IVAN BAXMEIER

Robert Ivan Baxmeier, M.D., F.A.C.P., of Pittsburgh, Pa., died June 27, 1946, of coronary thrombosis. Dr. Baxmeier was born in Pittsburgh, July 31, 1904. He received the degree of Bachelor of Science in 1926 at the University of Pittsburgh and the degree of Doctor of Medicine in 1930 from the Hahnemann Medical College of Philadelphia.

Following his internship in the Shadyside Hospital, Pittsburgh, Dr. Baxmeier continued his medical studies at the University of Chicago and in a number of courses presented by the American College of Physicians. He engaged in practice in Pittsburgh, devoting himself largely to Internal Medicine and Gastro-enterology. He became the Head of the Department of Gastro-enterology in the Shadyside Hospital.

Dr. Baxmeier was a member of the Allegheny County Medical Society of the State of Pennsylvania, Homeopathic Medical Society of the State of Pennsylvania, American Heart Association, and American Gastroscopic Club; he was also a Fellow of the American Medical Association, and became a Fellow of the American College of Physicians in 1944.

DR. TRIMBLE JOHNSON

Trimble Johnson, M.D., F.A.C.P., was born at Atlanta, Ga., on December 3, 1894. His elementary education was obtained in Atlanta schools and at the Staunton Military Academy. He took a pre-medical course at the Georgia School of Technology and his medical course at Emory University, from which he obtained the Doctor of Medicine degree in 1918. He served as intern at the Grady Memorial Hospital, Atlanta, and the Charity Hospital, New Orleans.

Dr. Johnson specialized in Internal Medicine and Gastro-enterology. He held appointments as Visiting Physician to the Grady Memorial Hospital and to the Anti-Tuberculosis Association Clinic and Good Samaritan Clinic, as well as to the Crawford W. Long Memorial Hospital.

Dr. Johnson became a Fellow of the American College of Physicians in 1929.

Dr. Johnson's death, attributable to pulmonary tuberculosis, occurred October 6, 1946.

DR. ISIDORE WILLIAM HELD

Dr. Isidore William Held, New York City, died at the Mount Sinai Hospital on Sunday, March 2, 1947, at the age of seventy.

Dr. Held was born in Boryslav, Austria, May 15, 1876. He received his medical degree from the Jefferson Medical College of Philadelphia in 1902, and took postgraduate work in Berlin and Vienna. Dr. Held was active in the practice of medicine in the vicinity of New York City. He was Consulting Physician at the Nathan and Miriam Barnert Memorial Hospital, Paterson, N. J.; at the Israel-Zion, Beth-El and Beth Moses Hospitals, Brooklyn; Jewish Memorial and Beth Israel Hospitals, Manhattan; and the Rockaway Beach Hospital, Queens. Dr. Held became Clinical Professor of Medicine in the New York University in 1935, a position which he held until 1941. In 1945 a Fellowship fund was contributed by a group of his friends to the University in his honor.

Dr. Held was the author of 86 monographs and articles on gastroenterology, hematology, roentgenology, cardiology and medical biography. In 1946, his medical work, "Peptic Ulcer," written in conjunction with Dr. A. Allen Goldbloom, was published.

Dr. Held was a Diplomate of the American Board of Internal Medicine; and a Fellow of the American College of Physicians since 1931, New York Academy of Medicine, American Medical Association and National Gastroenterological Association. He was a member of the American Heart Association, American Association for the Advancement of Science, Association of Military Surgeons, American-Soviet Medical Society and the State and County Medical Societies.

A Founder of the Federation for the Support of Jewish Philanthropic Societies of New York, Dr. Held was a member of the National Council of the American Jewish Joint Distribution Committee, and a founder of the American Jewish Physicians Committee.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York

DR. JOHN T. O'MARA

The College has just received information of the death, March 3, 1946, of John T. O'Mara, M.D., F.A.C.P. of Baltimore, Md.

Dr. O'Mara was born at Baltimore County, Md., in 1880. He attended Mount St. Joseph College and received his medical education at the Uni-

versity of Maryland School of Medicine and College of Physicians and Surgeons, graduating in 1903.

Dr. O'Mara served for many years on the Medical Staff of St. Agnes' Hospital and was at one time Chief of Staff.

Dr. O'Mara became a Fellow of The American College of Physicians in 1921. He was also a Fellow of the American Medical Association, and a member of the Baltimore City Medical Society, Medical and Chirurgical Faculty of Maryland, and the Southern Medical Association.

DR. MIGUEL ROSES–ARTAU

Miguel Roses-Artau, M.D., F.A.C.P., of San Juan, P. R., died in his residence on July 17, 1945, at the age of 71. At the time of his death he was still in active practice as Chief Radiologist to the Arecibo District Charity Hospital and the San Juan District Penitentiary.

Dr. Roses-Artau was born on August 9, 1874, in Palma de Mallorca, Spain. He came to Puerto Rico in his childhood and received his college and medical education at Maryland Medical College, graduating in 1904. For several years he worked in Arecibo, P. R. In 1912 he returned to Spain, where he pursued postgraduate work at the Pharmaceutical Institute of Barcelona. Upon his return to the island, he renewed his practice in the city of Arecibo, and later moved to San Juan.

During his first years in practice, Dr. Roses-Artau had the privilege of being one of the collaborators of Dr. Ashford in his work on schistosomiasis. Dr. Roses-Artau later devoted most of his time to the specialty of radiology, in which he performed a most conscientious job. He was appointed a member of the Insular Board of Health in 1926.

Dr. Roses-Artau became a Fellow of The American College of Physicians in 1926.

RAMON M. SUAREZ, M.D., F.A.C.P.,
Governor for Puerto Rico

DR. GEORGE ANDREW CHAPMAN

George Andrew Chapman, M.D., F.A.C.P., died December 16, 1946 at Glens Falls, N. Y., from uremia.

Dr. Chapman was born at Glens Falls in 1871. He received his medical education at the Baltimore Medical College, from which he obtained his degree in 1897. He undertook postgraduate studies at the University of Maryland Medical School in 1913.

Dr. Chapman was a veteran of the Spanish-American War. For many years he was the Health Officer of Queensbury. For many years also, he was affiliated, as Attending Physician, with the Glens Falls Hospital.

Dr. Chapman was a member of the American Public Health Association, American Association for the Advancement of Science, and the New York

State Society of Internal Medicine. He was a past President of the Medical Society of the State of New York and of the Warren County Medical Society. Dr. Chapman became a Fellow of the American College of Physicians in 1925.

Dr. Chapman's death at the age of 75 caused a distinct loss to the community in which he served.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

DR. HAROLD PHILLIPS HILL

Harold Phillips Hill, M.D., F.A.C.P., San Francisco, Calif., died December 3, 1946. His death marked the loss of another of the older and traditionally great internists of California. He was born in Waterbury, Vt., on August 5, 1877. His father, also a physician, practiced in Redlands, Calif., for over 40 years.

In 1898 Dr. Hill graduated with distinction from Stanford University, going from there to the University of California, where he received his M.D. degree in 1901.

From 1901 to 1902 he interned at St. Luke's Hospital in San Francisco, and was associated in practice in San Francisco with Dr. Clark J. Burnham from 1902 to 1908, when the latter moved to Berkeley.

Dr. Hill was Chief of the Medical Service at St. Luke's Hospital from 1905 to 1946. In 1913 he left the University of California, where he had served as Instructor in Physiology and Assistant Professor of Medicine, to become Clinical Professor of Medicine at the Stanford University School of Medicine. He was also appointed as Chief of Medicine on the Stanford Medical School Service at the San Francisco Hospital, where he held regular medical rounds and taught groups of students. His teaching was characterized by a very practical approach, and his painstaking and thorough examination of patients made a lasting impression on his students.

Dr. Hill's society memberships included the San Francisco County and California State Medical Societies; the American Medical Association; San Francisco Academy of Medicine. He became a Fellow of the American College of Physicians in 1932. In addition he was a member of the Phi Delta Theta, Nu Sigma Nu, Sigma Xi and Alpha Omega Alpha societies. He was a Diplomate of the American Board of Internal Medicine and a preceptor with the Board for several years.

As a consultant and teacher, Dr. Hill wielded a great influence in this community; his intense devotion to his patients and to the responsibilities of an outstanding teacher and internist remains as an example and inspiration to those of us who carry on in his stead.

ERNEST H. FALCONER, M.D., F.A.C.P.,
Governor for Northern California

DR. THOMAS HALL SHASTID

Dr. Thomas Hall Shastid, F.A.C.P., died of uremia, February 15, 1947, at Duluth, Minnesota. He was born in Pittsfield, Illinois on July 19, 1866. Dr. Shastid was a student at Eureka (Ill.) College, 1883–1886, at the Medical Department of Columbia University 1886–1887 and at the University of Vermont College of Medicine, from which he graduated with an M.D. degree in 1888. He pursued a course of postgraduate study at the University of Vienna, 1888–1889, and received an A.B. degree cum laude from Harvard University in 1893. Dr. Shastid received A.M. and LL.B. degrees from the University of Michigan in 1901 and 1902 respectively. He was certified by the American Board of Opthalmology in 1917 and received the honorary degree of Sc.D. from the University of Wisconsin in 1922. He began practice of medicine in Pittsfield, Illinois in 1889 and held the chair of Professor of the History of Medicine at the American Medical College of St. Louis from 1907 to 1912. In 1922 Dr. Shastid moved to Duluth, Minnesota where he became Consulting Ophthalmologist to St. Mary's and Miller Memorial Hospitals in Duluth, and St. Mary's Hospital in Superior, Wisconsin. He was also Visiting Ophthalmologist to St. Luke's Hospital, Duluth, Minnesota. He was a fellow of the A. M. A., American Academy of Medicine, American Medico-Legal and Toxicological Society, American Academy of Ophthalmology and Oto-Laryngology, American College of Surgeons, American College of Physicians and member of the American Association for Advancement of Science, National Society for Prevention of Blindness, American Association of the History of Medicine, International Congress of Ophthalmology, Author's League of America, Eugene Field Society, Societé Academique d'Histoire Internationale, Arts et Belles-Lettres and other societies. Dr. Shastid was the author of numerous scientific articles and several novels. He was the inventor of several instruments for the study and treatment of diseases of the eyes, ears, nose and throat and was a public lecturer on animals' eyes, light, blindness, permanent international peace and other subjects.

E. V. Allen, M.D., F.A.C.P.,
Governor for Minnesota